**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 100 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 100 mg of infliximab*. After reconstitution each mL contains 10 mg of infliximab.

* Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

Excipient with known effect

This medicine contains 0.5 mg polysorbate 80 (E433) in each vial.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate)

The powder is white.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Rheumatoid arthritis

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

Adult Crohn's disease

Remsima is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's disease

Remsima is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for

such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative colitis

Remsima is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

Remsima is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis

Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
Remsima should be administered:

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1).

Psoriasis

Remsima is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).

## 4.2 Posology and method of administration

Remsima treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, ankylosing spondylitis, psoriatic arthritis or psoriasis. Remsima should be administered intravenously. Remsima infusions should be administered by qualified healthcare professionals trained to detect any infusion-related issues. Patients treated with Remsima should be given the package leaflet and the patient reminder card.

During Remsima treatment, other concomitant therapies, e.g. corticosteroids and immunosuppressants should be optimised.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed. Remsima subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Posology

*Adults (≥18 years)*

*Rheumatoid arthritis*
3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Remsima must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, consideration may be given to increase the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

*Moderately to severely active Crohn's disease*
5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

In responding patients, the alternative strategies for continued treatment are:
- Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur (see 'Re-administration' below and section 4.4).

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

*Fistulising, active Crohn's disease*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given.

In responding patients, the alternative strategies for continued treatment are:
- Maintenance: Additional infusions of 5 mg/kg every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks (see 'Re-administration' below and section 4.4).

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

*Ulcerative colitis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

*Ankylosing spondylitis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

*Psoriatic arthritis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

*Psoriasis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

*Re-administration for Crohn's disease and rheumatoid arthritis*
If the signs and symptoms of disease recur, infliximab can be re-administered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year (see sections 4.4 and 4.8). The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

*Re-administration for ulcerative colitis*
The safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for ankylosing spondylitis*
The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for psoriatic arthritis*
The safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for psoriasis*
Limited experience from re-treatment with one single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen (see section 5.1).

Limited experience from re-treatment following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment (see section 4.8).

*Re-administration across indications*
In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen is not recommended (see section 4.8). In this situation, infliximab should be re-initiated as a single dose followed by the maintenance dose recommendations described above.

Special populations

*Elderly*

Specific studies of infliximab in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies. No dose adjustment is required (see section 5.2). For more information about the safety of infliximab in elderly patients (see sections 4.4 and 4.8).

*Renal and/or hepatic impairment*

Infliximab has not been studied in these patient populations. No dose recommendations can be made (see section 5.2).

*Paediatric population*

*Crohn's disease (6 to 17 years)*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment (see section 5.1).

Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should be carefully considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval.

The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.

*Ulcerative colitis (6 to 17 years)*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment (see section 5.1).

The safety and efficacy of infliximab have not been studied in children with ulcerative colitis below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.

*Psoriasis*
The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of psoriasis have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

*Juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis*
The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indications of juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

*Juvenile rheumatoid arthritis*
The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of juvenile rheumatoid arthritis have not been established. Currently available data are described in sections 4.8 and 5.2 but no recommendation on a posology can be made.

Method of administration

Infliximab should be administered intravenously over a 2-hour period. All patients administered infliximab are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously (see section 4.4).

*Shortened infusions across adult indications*

In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of infliximab (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses >6 mg/kg have not been studied (see section 4.8).

For preparation and administration instructions, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance, to other murine proteins, or to any of the excipients listed in section 6.1.

Patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see section 4.4).

Patients with moderate or severe heart failure (NYHA class III/IV) (see sections 4.4 and 4.8).

## 4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion reactions and hypersensitivity

Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions (see section 4.8).

Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically-treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot

always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered (see section 4.8).

In clinical studies, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval. Patients should be advised to seek immediate medical advice if they experience any delayed adverse reaction (see section 4.8). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with infliximab. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with infliximab must not be given if a patient develops a serious infection or sepsis.

Caution should be exercised when considering the use of infliximab in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Tumour necrosis factor alpha ($TNF_{\alpha}$) mediates inflammation and modulates cellular immune responses. Experimental data show that $TNF_{\alpha}$ is essential for the clearing of intracellular infections. Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab.

It should be noted that suppression of $TNF_{\alpha}$ may mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections and of typical clinical presentation of rare and unusual infections is critical in order to minimise delays in diagnosis and treatment.

Patients taking TNF-blockers are more susceptible to serious infections.

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis.

Patients who develop a new infection while undergoing treatment with infliximab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

*Tuberculosis*

There have been reports of active tuberculosis in patients receiving infliximab. It should be noted that in the majority of these reports tuberculosis was extrapulmonary, presenting as either local or disseminated disease.

Before starting treatment with infliximab, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, (e.g. tuberculin skin test, chest X-ray, and/or Interferon Gamma Release Assay), should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient reminder card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, infliximab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of infliximab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with antituberculosis therapy before the initiation of infliximab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, antituberculosis therapy should be considered before the initiation of infliximab.

Use of antituberculosis therapy should also be considered before the initiation of infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Some cases of active tuberculosis have been reported in patients treated with infliximab during and after treatment for latent tuberculosis.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after infliximab treatment.

*Invasive fungal infections*

In patients treated with infliximab, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness, and a physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients.

Invasive fungal infections may present as disseminated rather than localised disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of infliximab treatment should be carefully considered before initiation of infliximab therapy.

*Fistulising Crohn's disease*
Patients with fistulising Crohn's disease with acute suppurative fistulas must not initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded (see section 4.3).

Hepatitis B (HBV) reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with infliximab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with infliximab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with antiviral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, infliximab should be stopped and effective antiviral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥5 times the upper limit of normal develop(s), infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent administration of TNF-alpha inhibitor and anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another $TNF_{\alpha}$-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other $TNF_{\alpha}$-blocking agents. Therefore, the combination of infliximab and anakinra is not recommended.

Concurrent administration of TNF-alpha inhibitor and abatacept

In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of infliximab and abatacept is not recommended.

Concurrent administration with other biological therapeutics

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs

Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse reactions, including infection.

Vaccinations

It is recommended that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

In a subset of 90 adult patients with rheumatoid arthritis from the ASPIRE study a similar proportion of patients in each treatment group (methotrexate plus: placebo [n = 17], 3 mg/kg [n = 27] or 6 mg/kg infliximab [n = 46]) mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine, indicating that infliximab did not interfere with T-cell independent humoral immune responses. However, studies from the published literature in various indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) suggest that non-live vaccinations received during treatment with anti-TNF therapies, including infliximab may elicit a lower immune response than in patients not receiving anti-TNF therapy.

Live vaccines/therapeutic infectious agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with infliximab is not recommended.

Infant exposure *in utero*
In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see section 4.6).

Infant exposure via breast milk
Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see section 4.6).

Therapeutic infectious agents

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with infliximab.

Autoimmune processes

The relative deficiency of $TNF_{\alpha}$ caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab and is positive for antibodies against double-stranded DNA, further treatment with infliximab must not be given (see section 4.8).

Neurological events

Use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical studies of infliximab across all approved indications the incidence of lymphoma in infliximab-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

In an exploratory clinical study evaluating the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Caution should be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking.

With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded (see section 4.8). Caution should be

exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.8).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. Periodic screening should continue in women treated with infliximab, including those over 60 years of age.

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that infliximab treatment influences the risk for developing dysplasia or colon cancer.

Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits of continued therapy to the individual patients should be carefully considered by the clinician.

Heart failure

Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure (see sections 4.3 and 4.8).

Haematologic reactions

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of infliximab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Others

There is limited safety experience of infliximab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life of infliximab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on infliximab should be closely monitored for infections, and appropriate actions should be taken.

Failure to respond to treatment for Crohn's disease may indicate the presence of a fixed fibrotic stricture that may require surgical treatment. There is no evidence to suggest that infliximab worsens or causes fibrotic strictures.

Special populations

*Elderly*

The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly (see section 4.8).

*Paediatric population*

*Infections*
In clinical studies, infections have been reported in a higher proportion of paediatric patients compared to adult patients (see section 4.8).

*Vaccinations*
It is recommended that paediatric patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating infliximab therapy. Paediatric patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

*Malignancies and lymphoproliferative disorders*
Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.8).

Excipients with known effect

*Sodium content*

Remsima contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. Remsima is however, diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

*Polysorbate 80*

This medicine contains 0.5 mg of polysorbate 80 in each vial which is equivalent to 0.05 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.

Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent.

The combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended (see section 4.4).

It is recommended that live vaccines not be given concurrently with infliximab. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for 12 months following birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see section 4.4).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see sections 4.4 and 4.6).

It is recommended that therapeutic infectious agents not be given concurrently with infliximab (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Pregnancy

The moderate number of prospectively collected pregnancies exposed to infliximab resulting in live birth with known outcomes, including approximately 1,100 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

Based on an observational study from Northern Europe, an increased risk (OR, 95% CI; p-value) for C-section (1.50, 1.14-1.96; p = 0.0032), preterm birth (1.48, 1.05-2.09; p = 0.024), small for gestational age (2.79, 1.54-5.04; p = 0.0007), and low birth weight (2.03, 1.41-2.94; p = 0.0002) was observed in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids, 270 pregnancies) as compared to women exposed to immunomodulators and/or corticosteroids only (6,460 pregnancies). The potential contribution of exposure to infliximab and/or the severity of the underlying disease in these outcomes remains unclear.

Due to its inhibition of $TNF_{\alpha}$, infliximab administered during pregnancy could affect normal immune responses in the newborn. In a developmental toxicity study conducted in mice using an analogous

antibody that selectively inhibits the functional activity of mouse $TNF_{\alpha}$, there was no indication of maternal toxicity, embryotoxicity or teratogenicity (see section 5.3).

The available clinical experience is limited. Infliximab should only be used during pregnancy if clearly needed.

Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth (see sections 4.4 and 4.5). If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. Cases of agranulocytosis have also been reported (see section 4.8).

Breast-feeding

Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding.

Fertility

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Remsima may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of infliximab (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for infliximab include HBV reactivation, CHF (congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, paediatric malignancy, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease), and serious infusion reactions (see section 4.4).

Tabulated list of adverse reactions

Table 1 lists the ADRs based on experience from clinical studies as well as adverse reactions, some with fatal outcome, reported from post-marketing experience. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1**
**Adverse reactions in clinical studies and from post-marketing experience**

| | |
|---|---|
| *Infections and infestations* | |
| Very common: | Viral infection (e.g. influenza, herpes virus infection, COVID-19*). |
| Common: | Bacterial infections (e.g. sepsis, cellulitis, abscess). |
| Uncommon: | Tuberculosis, fungal infections (e.g. candidiasis, onychomycosis). |
| Rare: | Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation. |
| Not known: | Vaccine breakthrough infection (after *in utero* exposure to infliximab)*. |
| *Neoplasms benign, malignant and unspecified (including cysts and polyps)* | |
| Rare: | Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer. |
| Not known: | Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease and ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma. |
| *Blood and lymphatic system disorders* | |
| Common: | Neutropenia, leukopenia, anaemia, lymphadenopathy. |
| Uncommon: | Thrombocytopenia, lymphopenia, lymphocytosis. |
| Rare: | Agranulocytosis (including infants exposed *in utero* to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura. |
| *Immune system disorders* | |
| Common: | Allergic respiratory symptom. |
| Uncommon: | Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction. |
| Rare | Anaphylactic shock, vasculitis, sarcoid-like reaction |
| *Metabolism and nutrition disorders* | |
| Uncommon: | Dyslipidaemia. |
| *Psychiatric disorders* | |
| Common: | Depression, insomnia. |
| Uncommon: | Amnesia, agitation, confusion, somnolence, nervousness. |
| Rare: | Apathy. |
| *Nervous system disorders* | |
| Very common: | Headache. |
| Common: | Vertigo, dizziness, hypoaesthesia, paraesthesia. |
| Uncommon: | Seizure, neuropathy. |
| Rare: | Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy). |
| Not known: | Cerebrovascular accidents in close temporal association with infusion. |
| *Eye disorders* | |
| Common | Conjunctivitis |
| Uncommon | Keratitis, periorbital oedema, hordeolum |
| Rare | Endophthalmitis |
| Not known | Transient visual loss occurring during or within 2 hours of infusion |

| | |
|---|---|
| *Cardiac disorders* | |
| Common | Tachycardia, palpitation |
| Uncommon | Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia |
| Rare | Cyanosis, pericardial effusion |
| Not known | Myocardial ischaemia/myocardial infarction |
| *Vascular disorders* | |
| Common | Hypotension, hypertension, ecchymosis, hot flush, flushing |
| Uncommon | Peripheral ischaemia, thrombophlebitis, haematoma |
| Rare | Circulatory failure, petechia, vasospasm |
| *Respiratory, thoracic and mediastinal disorders* | |
| Very common | Upper respiratory tract infection, sinusitis |
| Common | Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis |
| Uncommon | Pulmonary oedema, bronchospasm, pleurisy, pleural effusion |
| Rare | Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis) |
| *Gastrointestinal disorders* | |
| Very common: | Abdominal pain, nausea |
| Common: | Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation |
| Uncommon | Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis |
| *Hepatobiliary disorders* | |
| Common: | Hepatic function abnormal, transaminases increased. |
| Uncommon: | Hepatitis, hepatocellular damage, cholecystitis. |
| Rare: | Autoimmune hepatitis, jaundice. |
| Not known: | Liver failure. |
| *Skin and subcutaneous tissue disorders* | |
| Common: | New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia. |
| Uncommon: | Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation. |
| Rare: | Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions. |
| Not known: | Worsening of symptoms of dermatomyositis. |
| *Musculoskeletal and connective tissue disorders* | |
| Common: | Arthralgia, myalgia, back pain. |
| *Renal and urinary disorders* | |
| Common: | Urinary tract infection. |
| Uncommon: | Pyelonephritis. |
| *Reproductive system and breast disorders* | |
| Uncommon: | Vaginitis. |

| | |
|---|---|
| *General disorders and administration site conditions* | |
| Very common: | Infusion-related reaction, pain. |
| Common: | Chest pain, fatigue, fever, injection site reaction, chills, oedema. |
| Uncommon: | Impaired healing. |
| Rare: | Granulomatous lesion. |
| *Investigations* | |
| Uncommon: | Autoantibody positive, weight increased[1]. |
| Rare: | Complement factor abnormal. |

* COVID-19 was seen with the SC administered Remsima

** including bovine tuberculosis (disseminated BCG infection), see section 4.4

[1] At month 12 of the controlled period for adult clinical trials across all indications, the median weight increase was 3.50 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects. The median weight increase for inflammatory bowel disease indications was 4.14 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects, and the median weight increase for rheumatology indications was 3.40 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects.

Description of selected adverse drug reactions

Infusion-related reactions

An infusion-related reaction was defined in clinical studies as any adverse event occurring during an infusion or within 1 hour after an infusion. In phase III clinical studies, 18% of infliximab-treated patients compared with 5% of placebo-treated patients experienced an infusion-related reaction. Overall, a higher proportion of patients receiving infliximab monotherapy experienced an infusion-related reaction compared to patients receiving infliximab with concomitant immunomodulators. Approximately 3% of patients discontinued treatment due to infusion-related reactions and all patients recovered with or without medical therapy. Of infliximab-treated patients who had an infusion reaction during the induction period, through week 6, 27% experienced an infusion reaction during the maintenance period, week 7 through week 54. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), infusions were to be administered over 2 hours for the first 3 infusions. The duration of subsequent infusions could be shortened to not less than 40 minutes in patients who did not experience serious infusion reactions. In this trial, sixty six percent of the patients (686 out of 1,040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1,040) received at least one shortened infusion of 60 minutes or less. Of the infliximab-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15% of patients and serious infusion reactions occurred in 0.4% of patients.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving infliximab monotherapy, 5% (9/179) of patients receiving infliximab in combination with AZA, and 5.6% (9/161) of patients receiving AZA monotherapy. One serious infusion reaction (<1%) occurred in a patient on infliximab monotherapy.

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with infliximab administration (see section 4.4). Cases of transient visual loss occurring during or within 2 hours of infliximab infusion have been reported. Events (some fatal) of myocardial ischaemia/infarction and arrhythmia have been reported, some in close temporal association with infusion of infliximab; cerebrovascular accidents have also been reported in close temporal association with infusion of infliximab.

Infusion reactions following re-administration of infliximab

A clinical study in patients with moderate to severe psoriasis was designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab (maximum of four infusions at 0, 2, 6 and 14 weeks) following disease flare. Patients did not receive any concomitant immunosuppressant therapy. In the re-treatment arm, 4% (8/219) of patients experienced a serious infusion reaction versus <1% (1/222) on maintenance therapy. The majority of serious infusion reactions occurred during the second infusion at week 2. The interval between the last maintenance dose and the first re-induction dose ranged from 35-231 days. Symptoms included, but were not limited to, dyspnoea, urticaria, facial oedema, and hypotension. In all cases, infliximab treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed hypersensitivity

In clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year. In the psoriasis studies, delayed hypersensitivity reactions occurred early in the treatment course. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients experiencing pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache.

There are insufficient data on the incidence of delayed hypersensitivity reactions after infliximab-free intervals of more than 1 year but limited data from clinical studies suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval (see section 4.4).

In a 1-year clinical study with repeated infusions in patients with Crohn's disease (ACCENT I study), the incidence of serum sickness-like reactions was 2.4%.

Immunogenicity

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion-related reactions.
In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 14% of patients with any immunosuppressant therapy, and in 24% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 8% of patients developed antibodies to infliximab. In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15% of patients (antibodies occurred in 4% of patients receiving methotrexate and in 26% of patients not receiving methotrexate at baseline). In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab (see section 4.4: "Infusion reactions and hypersensitivity").

Infections

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis (see section 4.4).

In clinical studies 36% of infliximab-treated patients were treated for infections compared with 25% of placebo-treated patients.

In rheumatoid arthritis clinical studies, the incidence of serious infections including pneumonia was higher in infliximab plus methotrexate-treated patients compared with methotrexate alone especially at doses of 6 mg/kg or greater (see section 4.4).

In post-marketing spontaneous reporting, infections are the most common serious adverse reaction. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported (see section 4.4).

Malignancies and lymphoproliferative disorders

In clinical studies with infliximab in which 5,780 patients were treated, representing 5,494 patient years, 5 cases of lymphomas and 26 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1,600 placebo-treated patients representing 941 patient years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6,234 patients-years (3,210 patients), 5 cases of lymphoma and 38 cases of non-lymphoma malignancies were reported.

Cases of malignancies, including lymphoma, have also been reported in the post-marketing setting (see section 4.4).

In an exploratory clinical study involving patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 adult patients were treated with infliximab at doses similar to those used in rheumatoid arthritis and Crohn's disease. Nine of these patients developed malignancies, including 1 lymphoma. The median duration of follow-up was 0.8 years (incidence 5.7% [95% CI 2.65%-10.6%]. There was one reported malignancy amongst 77 control patients (median duration of follow-up 0.8 years; incidence 1.3% [95% CI 0.03%-7.0%]). The majority of the malignancies developed in the lung or head and neck.

A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age (see section 4.4).

In addition, post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with infliximab with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, and most of whom were adolescent or young adult males (see section 4.4).

Heart failure

In a Phase II study aimed at evaluating infliximab in CHF, higher incidence of mortality due to worsening of heart failure were seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this study 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction ≤35%) were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Hepatobiliary events

In clinical studies, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT ≥5 x Upper Limit of Normal (ULN) have been observed (see Table 2). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant therapy. In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4).

**Table 2**
**Proportion of patients with increased ALT activity in clinical studies**

| Indication | Number of patients[3] | | Median follow-up (wks)[4] | | ≥3 x ULN | | ≥5 x ULN | |
|---|---|---|---|---|---|---|---|---|
| | placebo | infliximab | placebo | infliximab | placebo | infliximab | placebo | infliximab |
| Rheumatoid arthritis[1] | 375 | 1,087 | 58.1 | 58.3 | 3.2% | 3.9% | 0.8% | 0.9% |
| Crohn's disease[2] | 324 | 1,034 | 53.7 | 54.0 | 2.2% | 4.9% | 0.0% | 1.5% |
| Paediatric Crohn's disease | N/A | 139 | N/A | 53.0 | N/A | 4.4% | N/A | 1.5% |
| Ulcerative colitis | 242 | 482 | 30.1 | 30.8 | 1.2% | 2.5% | 0.4% | 0.6% |
| Paediatric Ulcerative colitis | N/A | 60 | N/A | 49.4 | N/A | 6.7% | N/A | 1.7% |
| Ankylosing spondylitis | 76 | 275 | 24.1 | 101.9 | 0.0% | 9.5% | 0.0% | 3.6% |
| Psoriatic arthritis | 98 | 191 | 18.1 | 39.1 | 0.0% | 6.8% | 0.0% | 2.1% |
| Plaque psoriasis | 281 | 1,175 | 16.1 | 50.1 | 0.4% | 7.7% | 0.0% | 3.4% |

1 Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
2 Placebo patients in the 2 Phase III studies in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomised to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day as active control in addition to placebo infliximab infusions.
3 Number of patients evaluated for ALT.
4 Median follow-up is based on patients treated.

Antinuclear antibodies (ANA)/Anti-double-stranded DNA (dsDNA) antibodies

Approximately half of infliximab-treated patients in clinical studies who were ANA negative at baseline developed a positive ANA during the study compared with approximately one fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of infliximab-treated patients compared with 0% of placebo-treated patients. At the last evaluation, 57% of infliximab-treated patients remained anti-dsDNA positive. Reports of lupus and lupus-like syndromes, however, remain uncommon (see section 4.4).

Paediatric population

*Juvenile rheumatoid arthritis patients*

Infliximab was studied in a clinical study in 120 patients (age range: 4-17 years old) with active juvenile rheumatoid arthritis despite methotrexate. Patients received 3 or 6 mg/kg infliximab as a 3-dose induction regimen (weeks 0, 2, 6 or weeks 14, 16, 20, respectively) followed by maintenance therapy every 8 weeks, in combination with methotrexate.

*Infusion reactions*
Infusion reactions occurred in 35% of patients with juvenile rheumatoid arthritis receiving 3 mg/kg compared with 17.5% of patients receiving 6 mg/kg. In the 3 mg/kg infliximab group, 4 out of 60 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg group, 2 out of 57 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction (see section 4.4).

*Immunogenicity*
Antibodies to infliximab developed in 38% of patients receiving 3 mg/kg compared with 12% of patients receiving 6 mg/kg. The antibody titres were notably higher for the 3 mg/kg compared to the 6 mg/kg group.

*Infections*
Infections occurred in 68% (41/60) of children receiving 3 mg/kg over 52 weeks, 65% (37/57) of children receiving infliximab 6 mg/kg over 38 weeks and 47% (28/60) of children receiving placebo over 14 weeks (see section 4.4).

*Paediatric Crohn's disease patients*

The following adverse reactions were reported more commonly in paediatric Crohn's disease patients in the REACH study (see section 5.1) than in adult Crohn's disease patients: anaemia (10.7%), blood in stool (9.7%), leukopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%). In addition, bone fracture (6.8%) was reported, however, a causal association has not been established. Other special considerations are discussed below.

*Infusion-related reactions*
In REACH, 17.5% of randomised patients experienced 1 or more infusion reactions. There were no serious infusion reactions, and 2 subjects in REACH had non-serious anaphylactic reactions.

*Immunogenicity*
Antibodies to infliximab were detected in 3 (2.9%) paediatric patients.

*Infections*
In the REACH study, infections were reported in 56.3% of randomised subjects treated with infliximab. Infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Three cases of pneumonia (1 serious) and 2 cases of herpes zoster (both non-serious) were reported.

*Paediatric ulcerative colitis patients*

Overall, the adverse reactions reported in the paediatric ulcerative colitis trial (C0168T72) and adult ulcerative colitis (ACT 1 and ACT 2) studies were generally consistent. In C0168T72, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever,

and headache. The most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on the q12 week vs. the q8 week dosing regimen.

*Infusion-related reactions*
Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the q8 week and 3 of 23 (13.0%) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

*Immunogenicity*
Antibodies to infliximab were detected in 4 (7.7%) patients through week 54.

*Infections*
Infections were reported in 31 (51.7%) of 60 treated patients in C0168T72 and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in C0168T72 was similar to that in the paediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). The overall incidence of infections in C0168T72 was 13/22 (59%) in the every 8 week maintenance treatment group and 14/23 (60.9%) in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%]) vs.15/60 [25.0%]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups. Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

Post-marketing experience

Post-marketing spontaneous serious adverse reactions with infliximab in the paediatric population have included malignancies including hepatosplenic T-cell lymphomas, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive auto-antibodies (see sections 4.4 and 4.8).

Other special populations

*Elderly*

In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in infliximab plus methotrexate-treated patients 65 years and older (11.3%) than in those under 65 years of age (4.6%). In patients treated with methotrexate alone, the incidence of serious infections was 5.2% in patients 65 years and older compared to 2.7% in patients under 65 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

No case of overdose has been reported. Single doses up to 20 mg/kg have been administered without toxic effects.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, tumour necrosis factor alpha ($TNF_\alpha$) inhibitors, ATC code: L04AB02

Remsima is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Mechanism of action

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of $TNF_\alpha$ but not to lymphotoxin α ($TNF_\beta$).

Pharmacodynamic effects

Infliximab inhibits the functional activity of $TNF_\alpha$ in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human $TNF_\alpha$ and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human $TNF_\alpha$, a process that parallels the loss of $TNF_\alpha$ bioactivity.

Elevated concentrations of $TNF_\alpha$ have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP), and increased haemoglobin levels in rheumatoid arthritis patients with reduced haemoglobin levels, compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalisation of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, short term treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin.

Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable $TNF_\alpha$. Infliximab treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, CRP. Total peripheral white blood cell counts were minimally affected in infliximab-treated patients, although changes in lymphocytes, monocytes and neutrophils reflected shifts towards normal ranges. Peripheral blood mononuclear cells (PBMC) from infliximab-treated patients showed undiminished proliferative responsiveness to stimuli compared with untreated patients, and no substantial changes in cytokine production by stimulated PBMC were observed following treatment with infliximab. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that infliximab treatment caused a reduction in the number of cells capable of expressing $TNF_\alpha$ and interferon γ. Additional histological studies provided evidence that treatment with infliximab reduces the infiltration of inflammatory cells into affected areas of the intestine and the presence of inflammation markers at these sites. Endoscopic studies of intestinal mucosa have shown evidence of mucosal healing in infliximab-treated patients.

Clinical efficacy and safety

*Adult rheumatoid arthritis*

The efficacy of infliximab was assessed in two multicentre, randomised, double-blind, pivotal clinical studies: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of the following 5 criteria: (1) evaluator's global assessment, (2) patient's global assessment, (3) functional/disability measure, (4) visual analogue pain scale and (5) erythrocyte sedimentation rate or C-reactive protein. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percent improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function.

The ATTRACT study evaluated responses at 30, 54 and 102 weeks in a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter. All patients were on stable methotrexate doses (median 15 mg/wk) for 6 months prior to enrolment and were to remain on stable doses throughout the study.

Results from week 54 (ACR20, total van der Heijde-modified Sharp score and HAQ) are shown in Table 3. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 3).

The effects observed at 54 weeks were maintained through 102 weeks. Due to a number of treatment withdrawals, the magnitude of the effect difference between infliximab and the methotrexate alone group cannot be defined.

**Table 3**
**Effects on ACR20, Structural Joint Damage and Physical Function at week 54, ATTRACT**

| | | Infliximab[b] | | | | |
|---|---|---|---|---|---|---|
| | Control[a] | 3 mg/kg q 8 wks | 3 mg/kg q 4 wks | 10 mg/kg q 8 wks | 10 mg/kg q 4 wks | All infliximab[b] |
| Patients with ACR20 response/Patients evaluated (%) | 15/88 (17%) | 36/86 (42%) | 41/86 (48%) | 51/87 (59%) | 48/81 (59%) | 176/340 (52%) |
| Total score[d] (van der Heijde-modified Sharp score) | | | | | | |
| Change from baseline (Mean ± SD[c]) | 7.0 ± 10.3 | 1.3 ± 6.0 | 1.6 ± 8.5 | 0.2 ± 3.6 | -0.7 ± 3.8 | 0.6 ± 5.9 |
| Median (Interquartile range) | 4.0 (0.5,9.7) | 0.5 (-1.5,3.0) | 0.1 (-2.5,3.0) | 0.5 (-1.5,2.0) | -0.5 (-3.0,1.5) | 0.0 (-1.8,2.0) |

| | Control[a] | Infliximab[b] | | | | |
|---|---|---|---|---|---|---|
| | | 3 mg/kg q 8 wks | 3 mg/kg q 4 wks | 10 mg/kg q 8 wks | 10 mg/kg q 4 wks | All infliximab[b] |
| Patients with no deterioration/patients evaluated (%)[c] | 13/64 (20%) | 34/71 (48%) | 35/71 (49%) | 37/77 (48%) | 44/66 (67%) | 150/285 (53%) |
| HAQ change from baseline over time[e] (patients evaluated) | 87 | 86 | 85 | 87 | 81 | 339 |
| Mean ± SD[c] | 0.2 ± 0.3 | 0.4 ± 0.3 | 0.5 ± 0.4 | 0.5 ± 0.5 | 0.4 ± 0.4 | 0.4 ± 0.4 |

a control = All patients had active RA despite treatment with stable methotrexate doses for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤10 mg/day) and/or NSAIDs was permitted, and folate supplementation was given.
b all infliximab doses given in combination with methotrexate and folate with some on corticosteroids and/or NSAIDs
c p <0.001, for each infliximab treatment group vs. control
d greater values indicate more joint damage.
e HAQ = Health Assessment Questionnaire; greater values indicate less disability.

The ASPIRE study evaluated responses at 54 weeks in 1,004 methotrexate naive patients with early (≤3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (optimised to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from week 54 are shown in Table 4.

After 54 weeks of treatment, both doses of infliximab + methotrexate resulted in statistically significantly greater improvement in signs and symptoms compared to methotrexate alone as measured by the proportion of patients achieving ACR20, 50 and 70 responses.

In ASPIRE, more than 90% of patients had at least two evaluable X-rays. Reduction in the rate of progression of structural damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone.

**Table 4**
**Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE**

| | | Infliximab + MTX | | |
|---|---|---|---|---|
| | Placebo + MTX | 3 mg/kg | 6 mg/kg | Combined |
| Subjects randomised | 282 | 359 | 363 | 722 |
| Percentage ACR improvement | | | | |
| Mean ± SD[a] | 24.8 ± 59.7 | 37.3 ± 52.8 | 42.0 ± 47.3 | 39.6 ± 50.1 |
| Change from baseline in total van der Heijde-modified Sharp score[b] | | | | |
| Mean ± SD[a] | 3.70 ± 9.61 | 0.42 ± 5.82 | 0.51 ± 5.55 | 0.46 ± 5.68 |
| Median | 0.43 | 0.00 | 0.00 | 0.00 |
| Improvement from baseline in HAQ averaged over time from week 30 to week 54[c] | | | | |
| Mean ± SD[d] | 0.68 ± 0.63 | 0.80 ± 0.65 | 0.88 ± 0.65 | 0.84 ± 0.65 |

a p <0.001, for each infliximab treatment group vs control.
b greater values indicate more joint damage.
c HAQ = Health Assessment Questionnaire; greater values indicate less disability.
d p = 0.030 and <0.001 for the 3 mg/kg and 6 mg/kg treatment groups respectively vs. placebo + MTX.

Data to support dose titration in rheumatoid arthritis come from ATTRACT, ASPIRE and the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the study arms (group 2, n=329), patients with an inadequate response were allowed to dose titrate with 1.5 mg/kg increments from 3 up to 9 mg/kg. The majority (67%) of these patients did not require

any dose titration. Of the patients who required a dose titration, 80% achieved clinical response and the majority (64%) of these required only one adjustment of 1.5 mg/kg.

*Adult Crohn's disease*

*Induction treatment in moderately to severely active Crohn's disease*
The efficacy of a single dose treatment with infliximab was assessed in 108 patients with active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥220 ≤400) in a randomised, double-blinded, placebo-controlled, dose-response study. Of these 108 patients, 27 were treated with the recommended dosage of infliximab 5 mg/kg. All patients had experienced an inadequate response to prior conventional therapies. Concurrent use of stable doses of conventional therapies was permitted, and 92% of patients continued to receive these therapies.

The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥70 points from baseline at the 4-week evaluation and without an increase in the use of medicinal products or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients in clinical remission at week 4 (CDAI <150) and clinical response over time.

At week 4, following administration of a single dose, 22/27 (81%) of infliximab-treated patients receiving a 5 mg/kg dose achieved a clinical response vs. 4/25 (16%) of the placebo-treated patients ($p < 0.001$). Also at week 4, 13/27 (48%) of infliximab-treated patients achieved a clinical remission (CDAI <150) vs. 1/25 (4%) of placebo-treated patients. A response was observed within 2 weeks, with a maximum response at 4 weeks. At the last observation at 12 weeks, 13/27 (48%) of infliximab-treated patients were still responding.

*Maintenance treatment in moderately to severely active Crohn's disease in adults*
The efficacy of repeated infusions with infliximab was studied in a 1-year clinical study (ACCENT I). A total of 573 patients with moderately to severely active Crohn's disease (CDAI ≥220 ≤400) received a single infusion of 5 mg/kg at week 0. 178 of the 580 enrolled patients (30.7%) were defined as having severe disease (CDAI score > 300 and concomitant corticosteroid and/or immunosuppressants) corresponding to the population defined in the indication (see section 4.1). At week 2, all patients were assessed for clinical response and randomised to one of 3 treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group. All 3 groups received repeated infusions at week 2, 6 and every 8 weeks thereafter.

Of the 573 patients randomised, 335 (58%) achieved clinical response by week 2. These patients were classified as week-2 responders and were included in the primary analysis (see Table 5). Among patients classified as non-responders at week 2, 32% (26/81) in the placebo maintenance group and 42% (68/163) in the infliximab group achieved clinical response by week 6. There was no difference between groups in the number of late responders thereafter.

The co-primary endpoints were the proportion of patients in clinical remission (CDAI <150) at week 30 and time to loss of response through week 54. Corticosteroid tapering was permitted after week 6.

**Table 5**
**Effects on response and remission rate, data from ACCENT I (Week-2 responders)**

| | ACCENT I (Week-2 responders) % of patients | | |
|---|---|---|---|
| | Placebo Maintenance (n=110) | Infliximab Maintenance 5 mg/kg (n=113) (p value) | Infliximab Maintenance 10 mg/kg (n=112) (p value) |
| Median time to loss of response through week 54 | 19 weeks | 38 weeks (0.002) | >54 weeks (<0.001) |
| **Week 30** | | | |
| Clinical Response[a] | 27.3 | 51.3 (<0.001) | 59.1 (<0.001) |
| Clinical Remission | 20.9 | 38.9 (0.003) | 45.5 (<0.001) |
| Steroid-Free Remission | 10.7 (6/56) | 31.0 (18/58) (0.008) | 36.8 (21/57) (0.001) |
| **Week 54** | | | |
| Clinical Response[a] | 15.5 | 38.1 (<0.001) | 47.7 (<0.001) |
| Clinical Remission | 13.6 | 28.3 (0.007) | 38.4 (<0.001) |
| Sustained Steroid-Free Remission[b] | 5.7 (3/53) | 17.9 (10/56) (0.075) | 28.6 (16/56) (0.002) |

a Reduction in CDAI ≥25% and ≥70 points.
b CDAI <150 at both Week 30 and 54 and not receiving corticosteroids in the 3 months prior to Week 54 among patients who were receiving corticosteroids at baseline.

Beginning at week 14, patients who had responded to treatment, but subsequently lost their clinical benefit, were allowed to cross over to a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Eighty nine percent (50/56) of patients who lost clinical response on infliximab 5 mg/kg maintenance therapy after week 14 responded to treatment with infliximab 10 mg/kg.

Improvements in quality of life measures, a reduction in disease-related hospitalisations and corticosteroid use were seen in the infliximab maintenance groups compared with the placebo maintenance group at weeks 30 and 54.

Infliximab with or without AZA was assessed in a randomised, double-blind, active comparator study (SONIC) of 508 adult patients with moderate to severe Crohn's disease (CDAI ≥220 ≤450) who were naive to biologics and immunosuppressants and had a median disease duration of 2.3 years. At baseline 27.4% of patients were receiving systemic corticosteroids, 14.2% of patients were receiving budesonide, and 54.3% of patients were receiving 5-ASA compounds. Patients were randomised to receive AZA monotherapy, infliximab monotherapy, or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily.

The primary endpoint of the study was corticosteroid-free clinical remission at week 26, defined as patients in clinical remission (CDAI of <150) who, for at least 3 weeks, had not taken oral systemic corticosteroids (prednisone or equivalent) or budesonide at a dose >6 mg/day. For results see Table 6. The proportions of patients with mucosal healing at week 26 were significantly greater in the infliximab plus AZA combination (43.9%, p<0.001) and infliximab monotherapy groups (30.1%, p=0.023) compared to the AZA monotherapy group (16.5%).

**Table 6**
**Percent of patients achieving corticosteroid-free clinical remission at Week 26, SONIC**

| | AZA Monotherapy | Infliximab Monotherapy | Infliximab + AZA Combination therapy |
|---|---|---|---|
| **Week 26** | | | |
| All randomised patients | 30.0% (51/170) | 44.4% (75/169) (p=0.006)* | 56.8% (96/169) (p<0.001)* |

* p-values represent each infliximab treatment group vs. AZA monotherapy.

Similar trends in the achievement of corticosteroid-free clinical remission were observed at week 50. Furthermore, improved quality of life as measured by IBDQ was observed with infliximab.

*Induction treatment in fistulising active Crohn's disease*
The efficacy was assessed in a randomised, double-blinded, placebo-controlled study in 94 patients with fistulising Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty one of these patients were treated with infliximab 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these therapies. Patients received three doses of either placebo or infliximab at weeks 0, 2 and 6. Patients were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistulae draining upon gentle compression on at least two consecutive visits (4 weeks apart), without an increase in the use of medicinal products or surgery for Crohn's disease.

Sixty eight percent (21/31) of infliximab-treated patients receiving a 5 mg/kg dose regimen achieved a clinical response vs. 26% (8/31) placebo-treated patients (p=0.002). The median time to onset of response in the infliximab-treated group was 2 weeks. The median duration of response was 12 weeks. Additionally, closure of all fistulae was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients (p=0.001).

*Maintenance treatment in fistulising active Crohn's disease*
The efficacy of repeated infusions with infliximab in patients with fistulising Crohn's disease was studied in a 1-year clinical study (ACCENT II). A total of 306 patients received 3 doses of infliximab 5 mg/kg at week 0, 2 and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. At week 14, 282 patients were assessed for clinical response and randomised to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46.

Week-14 responders (195/282) were analysed for the primary endpoint, which was time from randomisation to loss of response (see Table 7). Corticosteroid tapering was permitted after week 6.

**Table 7**
**Effects on response rate, data from ACCENT II (Week-14 responders)**

| | ACCENT II (Week-14 responders) | | |
|---|---|---|---|
| | Placebo Maintenance (n=99) | Infliximab Maintenance (5 mg/kg) (n=96) | p-value |
| Median time to loss of response through week 54 | 14 weeks | >40 weeks | <0.001 |
| **Week 54** | | | |
| Fistula Response (%)[a] | 23.5 | 46.2 | 0.001 |
| Complete fistula response (%)[b] | 19.4 | 36.3 | 0.009 |

a A ≥50% reduction from baseline in the number of draining fistulas over a period of ≥4 weeks.
b Absence of any draining fistulas.

Beginning at week 22, patients who initially responded to treatment and subsequently lost their response were eligible to cross over to active re-treatment every 8 weeks at a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Among patients in the infliximab 5 mg/kg group who crossed over because of loss of fistula response after week 22, 57% (12/21) responded to re-treatment with infliximab 10 mg/kg every 8 weeks.

There was no significant difference between placebo and infliximab for the proportion of patients with sustained closure of all fistulas through week 54, for symptoms such as proctalgia, abscesses and urinary tract infection or for number of newly developed fistulas during treatment.

Maintenance therapy with infliximab every 8 weeks significantly reduced disease-related hospitalisations and surgeries compared with placebo. Furthermore, a reduction in corticosteroid use and improvements in quality of life were observed.

*Adult ulcerative colitis*

The safety and efficacy of infliximab were assessed in two (ACT 1 and ACT 2) randomised, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥2) with an inadequate response to conventional therapies [oral corticosteroids, aminosalicylates and/or immunomodulators (6-MP, AZA)]. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In both studies, patients were randomised to receive either placebo, 5 mg/kg infliximab, or 10 mg/kg infliximab at weeks 0, 2, 6, 14 and 22, and in ACT 1 at weeks 30, 38 and 46. Corticosteroid taper was permitted after week 8.

**Table 8**
**Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2**

| | | Infliximab | | |
|---|---|---|---|---|
| | Placebo | 5 mg/kg | 10 mg/kg | Combined |
| Subjects randomised | 244 | 242 | 242 | 484 |
| **Percentage of subjects in clinical response and in sustained clinical response** | | | | |
| Clinical response at Week 8[a] | 33.2% | 66.9% | 65.3% | 66.1% |
| Clinical response at Week 30[a] | 27.9% | 49.6% | 55.4% | 52.5% |
| Sustained response (clinical response at both Week 8 and Week 30)[a] | 19.3% | 45.0% | 49.6% | 47.3% |
| **Percentage of subjects in clinical remission and sustained remission** | | | | |
| Clinical remission at Week 8[a] | 10.2% | 36.4% | 29.8% | 33.1% |
| Clinical remission at Week 30[a] | 13.1% | 29.8% | 36.4% | 33.1% |
| Sustained remission(in remission at both Week 8 and Week 30)[a] | 5.3% | 19.0% | 24.4% | 21.7% |
| **Percentage of subjects with mucosal healing** | | | | |
| Mucosal healing at Week 8[a] | 32.4% | 61.2% | 60.3% | 60.7% |
| Mucosal healing at Week 30[a] | 27.5% | 48.3% | 52.9% | 50.6% |

a $p < 0.001$, for each infliximab treatment group vs. placebo.

The efficacy of infliximab through week 54 was assessed in the ACT 1 study.
At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p<0.001$). Clinical remission and mucosal healing occurred in a greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.6% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportions of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in the placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

A greater proportion of patients in the combined infliximab treatment group were able to discontinue corticosteroids while remaining in clinical remission compared to the placebo treatment group at both week 30 (22.3% vs. 7.2%, p <0.001, pooled ACT 1 & ACT 2 data) and week 54 (21.0% vs. 8.9%, p=0.022, ACT 1 data).

The pooled data analysis from the ACT 1 and ACT 2 studies and their extensions, analysed from baseline through 54 weeks, demonstrated a reduction of ulcerative colitis-related hospitalisations and surgical procedures with infliximab treatment. The number of ulcerative colitis-related hospitalisations was significantly lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of hospitalisations per 100 subject-years: 21 and 19 vs. 40 in the placebo group; p=0.019 and p=0.007, respectively). The number of ulcerative colitis-related surgical procedures was also lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of surgical procedures per 100 subject-years: 22 and 19 vs. 34*;* p=0.145 and p=0.022, respectively).

The proportion of subjects who underwent colectomy at any time within 54 weeks following the first infusion of study agent were collected and pooled from the ACT 1 and ACT 2 studies and their extensions. Fewer subjects underwent colectomy in the 5 mg/kg infliximab group (28/242 or 11.6% [N.S.]) and the 10 mg/kg infliximab group (18/242 or 7.4% [p=0.011]) than in the placebo group (36/244; 14.8%).

The reduction in incidence of colectomy was also examined in another randomised, double-blind study (C0168Y06) in hospitalised patients (n=45) with moderately to severely active ulcerative colitis who failed to respond to intravenous corticosteroids and who were therefore at higher risk for colectomy. Significantly fewer colectomies occurred within 3 months of study infusion in patients who received a single dose of 5 mg/kg infliximab compared to patients who received placebo (29.2% vs. 66.7% respectively, p=0.017).

In ACT 1 and ACT 2, infliximab improved quality of life, confirmed by statistically significant improvement in both a disease specific measure, IBDQ, and by improvement in the generic 36-item short form survey SF-36.

*Adult ankylosing spondylitis*

Efficacy and safety of infliximab were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain ≥ 4 on a scale of 1-10).

In the first study (P01522), which had a 3 month double-blind phase, 70 patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). At week 12, placebo patients were switched to infliximab 5 mg/kg every 6 weeks up to week 54. After the first year of the study, 53 patients continued into an open-label extension to week 102.

In the second clinical study (ASSERT), 279 patients were randomised to receive either placebo (Group 1, n=78) or 5 mg/kg infliximab (Group 2, n=201) at 0, 2 and 6 weeks and every 6 weeks to week 24. Thereafter, all subjects continued on infliximab every 6 weeks to week 96. Group 1 received 5 mg/kg infliximab. In Group 2, starting with the week 36 infusion, patients who had a BASDAI ≥3 at 2 consecutive visits, received 7.5 mg/kg infliximab every 6 weeks thereafter through week 96.

In ASSERT, improvement in signs and symptoms was observed as early as week 2. At week 24, the number of ASAS 20 responders was 15/78 (19%) in the placebo group, and 123/201 (61%) in the 5 mg/kg infliximab group (p<0.001). There were 95 subjects from group 2 who continued on 5 mg/kg every 6 weeks. At 102 weeks there were 80 subjects still on infliximab treatment and among those, 71 (89%) were ASAS 20 responders.

In P01522, improvement in signs and symptoms was also observed as early as week 2. At week 12, the number of BASDAI 50 responders were 3/35 (9%) in the placebo group, and 20/35 (57%) in the 5 mg/kg group (p<0.01). There were 53 subjects who continued on 5 mg/kg every 6 weeks. At

102 weeks there were 49 subjects still on infliximab treatment and among those, 30 (61%) were BASDAI 50 responders.

In both studies, physical function and quality of life as measured by the BASFI and the physical component score of the SF-36 were also improved significantly.

*Adult psoriatic arthritis*

Efficacy and safety were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active psoriatic arthritis.

In the first clinical study (IMPACT), efficacy and safety of infliximab were studied in 104 patients with active polyarticular psoriatic arthritis. During the 16-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, and 14 (52 patients in each group). Starting at week 16, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 8 weeks up to week 46. After the first year of the study, 78 patients continued into an open-label extension to week 98.

In the second clinical study (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints). Forty six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, 47 placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46.

Key efficacy results for IMPACT and IMPACT 2 are shown in Table 9 below:

**Table 9**
**Effects on ACR and PASI in IMPACT and IMPACT 2**

| | IMPACT | | | IMPACT 2* | | |
|---|---|---|---|---|---|---|
| | Placebo (Week 16) | Infliximab (Week 16) | Infliximab (Week 98) | Placebo (Week 24) | Infliximab (Week 24) | Infliximab (Week 54) |
| Patients randomised | 52 | 52 | N/A[a] | 100 | 100 | 100 |
| ACR response (% of patients) N | 52 | 52 | 78 | 100 | 100 | 100 |
| ACR 20 response* | 5 (10%) | 34 (65%) | 48 (62%) | 16 (16%) | 54 (54%) | 53 (53%) |
| ACR 50 response* | 0 (0%) | 24 (46%) | 35 (45%) | 4 (4%) | 41 (41%) | 33 (33%) |
| ACR 70 response* | 0 (0%) | 15 (29%) | 27 (35%) | 2 (2%) | 27 (27%) | 20 (20%) |
| PASI response (% of patients)[b] N | | | | 87 | 83 | 82 |
| PASI 75 response** | | | | 1 (1%) | 50 (60%) | 40 (48.8%) |

* ITT-analysis where subjects with missing data were included as non-responders.
a Week 98 data for IMPACT includes combined placebo crossover and infliximab patients who entered the open-label extension.

b Based on patients with PASI >2.5 at baseline for IMPACT, and patients with >3% BSA psoriasis skin involvement at baseline in IMPACT 2.

** PASI 75 response for IMPACT not included due to low N; p<0.001 for infliximab vs. placebo at week 24 for IMPACT 2.

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54, respectively. Efficacy has been demonstrated with or without concomitant use of methotrexate. Decreases in parameters of peripheral activity characteristic of psoriatic arthritis (such as number of swollen joints, number of painful/tender joints, dactylitis and presence of enthesopathy) were seen in the infliximab-treated patients.

Radiographic changes were assessed in IMPACT 2. Radiographs of hands and feet were collected at baseline, weeks 24 and 54. Infliximab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at the week 24 primary endpoint as measured by change from baseline in total modified vdH-S score (mean ± SD score was 0.82 ± 2.62 in the placebo group compared with -0.70 ± 2.53 in the infliximab group; p<0.001). In the infliximab group, the mean change in total modified vdH-S score remained below 0 at the week 54 timepoint.

Infliximab-treated patients demonstrated significant improvement in physical function as assessed by HAQ. Significant improvements in health-related quality of life were also demonstrated as measured by the physical and mental component summary scores of the SF-36 in IMPACT 2.

*Adult psoriasis*

The efficacy of infliximab was assessed in two multicentre, randomised, double-blind studies: SPIRIT and EXPRESS. Patients in both studies had plaque psoriasis (Body Surface Area [BSA] ≥10% and Psoriasis Area and Severity Index [PASI] score ≥12). The primary endpoint in both studies was the percent of patients who achieved ≥75% improvement in PASI from baseline at week 10.

SPIRIT evaluated the efficacy of infliximab induction therapy in 249 patients with plaque psoriasis that had previously received PUVA or systemic therapy. Patients received either 3 or 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6. Patients with a PGA score ≥3 were eligible to receive an additional infusion of the same treatment at week 26.
In SPIRIT, the proportion of patients achieving PASI 75 at week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group (p<0.001). By week 26, twenty weeks after the last induction dose, 30% of patients in the 5 mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of >20 weeks. No rebound was observed.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis. Patients received 5 mg/kg infliximab- or placebo-infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8 weeks through week 22 in the placebo group and through week 46 in the infliximab group. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg). Nail psoriasis was assessed using the Nail Psoriasis Severity Index (NAPSI). Prior therapy with PUVA, methotrexate, ciclosporin, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in Table 10. In infliximab treated subjects, significant PASI 50 responses were apparent at the first visit (week 2) and PASI 75 responses by the second visit (week 6). Efficacy was similar in the subgroup of patients that were exposed to previous systemic therapies compared to the overall study population.

**Table 10**
**Summary of PASI response, PGA response and percent of patients with all nails cleared at Weeks 10, 24 and 50. EXPRESS**

| | Placebo → Infliximab 5 mg/kg (at week 24) | Infliximab 5 mg/kg |
|---|---|---|
| **Week 10** | | |
| N | 77 | 301 |
| ≥90% improvement | 1 (1.3%) | 172 (57.1%) [a] |
| ≥75% improvement | 2 (2.6%) | 242 (80.4%) [a] |
| ≥50% improvement | 6 (7.8%) | 274 (91.0%) |
| PGA of cleared (0) or minimal (1) | 3 (3.9%) | 242 (82.9%) [ab] |
| PGA of cleared (0), minimal (1), or mild (2) | 14 (18.2%) | 275 (94.2%) [ab] |
| **Week 24** | | |
| N | 77 | 276 |
| ≥90% improvement | 1 (1.3%) | 161 (58.3%) [a] |
| ≥75% improvement | 3 (3.9%) | 227 (82.2%) [a] |
| ≥50% improvement | 5 (6.5%) | 248 (89.9%) |
| PGA of cleared (0) or minimal (1) | 2 (2.6%) | 203 (73.6%) [a] |
| PGA of cleared (0), minimal (1), or mild (2) | 15 (19.5%) | 246 (89.1%) [a] |
| **Week 50** | | |
| N | 68 | 281 |
| ≥90% improvement | 34 (50.0%) | 127 (45.2%) |
| ≥75% improvement | 52 (76.5%) | 170 (60.5%) |
| ≥50% improvement | 61 (89.7%) | 193 (68.7%) |
| PGA of cleared (0) or minimal (1) | 46 (67.6%) | 149 (53.0%) |
| PGA of cleared (0), minimal (1), or mild (2) | 59 (86.8%) | 189 (67.3%) |
| **All nails cleared[c]** | | |
| Week 10 | 1/65(1.5%) | 16/235 (6.8%) |
| Week 24 | 3/65 (4.6%) | 58/223 (26.0%) [a] |
| Week 50 | 27/64 (42.2%) | 92/226 (40.7%) |

a p <0.001, for each infliximab treatment group vs. control.
b n = 292.
c Analysis was based on subjects with nail psoriasis at baseline (81.8% of subjects). Mean baseline NAPSI scores were 4.6 and 4.3 in infliximab and placebo group.

Significant improvements from baseline were demonstrated in DLQI (p<0.001) and the physical and mental component scores of the SF 36 (p<0.001 for each component comparison).

Paediatric population

*Paediatric Crohn's disease (6 to 17 years)*

In the REACH study, 112 patients (6 to 17 years, median age 13.0 years) with moderate to severe, active Crohn's disease (median paediatric CDAI of 40) and an inadequate response to conventional therapies were to receive 5 mg/kg infliximab at weeks 0, 2, and 6. All patients were required to be on a stable dose of 6-MP, AZA or MTX (35% were also receiving corticosteroids at baseline). Patients assessed by the investigator to be in clinical response at week 10 were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose (10 mg/kg) and/or shorter dosing interval (q8 weeks) was allowed. Thirty two (32) evaluable paediatric patients crossed over (9 subjects in the q8 weeks and 23 subjects in the q12 weeks maintenance groups). Twenty four of these patients (75.0%) regained clinical response after crossing over.

The proportion of subjects in clinical response at week 10 was 88.4% (99/112). The proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112).
At week 30, the proportion of subjects in clinical remission was higher in the q8 week (59.6%, 31/52) than the q12 week maintenance treatment group (35.3%, 18/51; p=0.013). At week 54, the figures were 55.8% (29/52) and 23.5% (12/51) in the q8 weeks and q12 weeks maintenance groups, respectively ($p < 0.001$).
Data about fistulas were derived from PCDAI scores. Of the 22 subjects that had fistulas at baseline, 63.6% (14/22), 59.1% (13/22) and 68.2% (15/22) were in complete fistula response at week 10, 30 and 54, respectively, in the combined q8 weeks and q12 weeks maintenance groups.

In addition, statistically and clinically significant improvements in quality of life and height, as well as a significant reduction in corticosteroid use, were observed versus baseline.

*Paediatric ulcerative colitis (6 to 17 years)*

The safety and efficacy of infliximab were assessed in a multicentre, randomised, open-label, parallel-group clinical study (C0168T72) in 60 paediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; endoscopic subscore $\geq 2$) with an inadequate response to conventional therapies. At baseline 53% of patients were receiving immunomodulator therapy (6-MP, AZA and/or MTX) and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after week 0.

All patients received an induction regimen of 5 mg/kg infliximab at weeks 0, 2, and 6. Patients who did not respond to infliximab at week 8 (n=15) received no further medicinal product and returned for safety follow-up. At week 8, 45 patients were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen.

The proportion of patients in clinical response at week 8 was 73.3% (44/60). Clinical response at week 8 was similar between those with or without concomitant immunomodulator use at baseline. Clinical remission at week 8 was 33.3% (17/51) as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) score.

At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance group and 18% (4/22) in the q12 week maintenance treatment group. For patients receiving corticosteroids at baseline, the proportion of patients in remission and not receiving corticosteroids at week 54 was 38.5% (5/13) for the q8 week and 0% (0/13) for the q12 week maintenance treatment group.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 vs.15/60). While the numbers of patients in each subgroup are too small to draw definitive conclusions about the effect of age, there was a higher number of patients in the younger age group who stepped up in dose or discontinued treatment due to inadequate efficacy.

*Other paediatric indications*

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing infliximab in all subsets of the paediatric population in rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and Crohn's disease (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration ($C_{max}$) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median $V_d$ of 3.0 to 4.1 litres) was not dependent

on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. No time-dependency of the Pharmacokinetics was observed. The elimination pathways for infliximab have not been characterised. Unchanged infliximab was not detected in urine. No major age- or weight-related differences in clearance or volume of distribution were observed in rheumatoid arthritis patients. The pharmacokinetics of infliximab in elderly patients has not been studied. Studies have not been performed in patients with liver or renal disease.

At single doses of 3, 5, or 10 mg/kg, the median $C_{max}$ values were 77, 118 and 277 micrograms/mL, respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after the recommended single dose of 5 mg/kg for Crohn's disease and the rheumatoid arthritis maintenance dose of 3 mg/kg every 8 weeks.

Repeated administration of infliximab (5 mg/kg at 0, 2 and 6 weeks in fistulising Crohn's disease, 3 or 10 mg/kg every 4 or 8 weeks in rheumatoid arthritis) resulted in a slight accumulation of infliximab in serum after the second dose. No further clinically relevant accumulation was observed. In most fistulising Crohn's disease patients, infliximab was detected in serum for 12 weeks (range 4-28 weeks) after administration of the regimen.

Paediatric population

Population pharmacokinetic analysis based on data obtained from patients with ulcerative colitis (N=60), Crohn's disease (N=112), juvenile rheumatoid arthritis (N=117) and Kawasaki disease (N=16) with an overall age range from 2 months to 17 years indicated that exposure to infliximab was dependent on body weight in a non-linear way. Following administration of 5 mg/kg infliximab every 8 weeks, the predicted median steady-state infliximab exposure (area under concentration-time curve at steady state, AUCss) in paediatric patients aged 6 years to 17 years was approximately 20% lower than the predicted median steady-state medicinal product exposure in adults. The median AUCss in paediatric patients aged 2 years to less than 6 years was predicted to be approximately 40% lower than that in adults, although the number of patients supporting this estimate is limited.

### 5.3 Preclinical safety data

Infliximab does not cross react with $TNF_{\alpha}$ from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse $TNF_{\alpha}$, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse $TNF_{\alpha}$, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.

Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in $TNF_{\alpha}$ demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sucrose
Polysorbate 80 (E433)
Sodium dihydrogen phosphate monohydrate
Disodium phosphate dihydrate

## 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## 6.3 Shelf life

Before reconstitution:

5 years at 2°C – 8°C.

Remsima may be stored at temperatures up to a maximum of 25°C for a single period of up to 6 months, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Remsima must not be returned to refrigerated storage.

After reconstitution and dilution:

Chemical and physical in use stability of the diluted solution has been demonstrated for up to 60 days at 2 °C to 8 °C and for an additional 24 hours at 25°C after removal from refrigeration. From a microbiological point of view, the infusion solution should be administered immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has been taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions up to 25°C before reconstitution of the medicinal product, see section 6.3.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Type 1 glass vial with a (butyl) rubber stopper and an aluminium seal with a flip-off button.

Pack sizes of 1, 2, 3, 4, 5 vials.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

1. The dose and the number of Remsima vials have to be calculated. Each Remsima vial contains 100 mg infliximab. The required total volume of reconstituted Remsima solution has to be calculated.

2. Under aseptic conditions, each Remsima vial should be reconstituted with 10 mL of water for injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. The flip-top from the vial has to be removed and the top has to be wiped with a 70% alcohol swab. The syringe needle should be inserted into the vial through the centre of the rubber stopper and the stream of water for injections directed to the glass wall of the vial. The solution has to be gently swirled by rotating the vial to dissolve the powder. Prolonged or vigorous agitation must be avoided. THE VIAL MUST NOT BE SHAKEN. Foaming of the solution on reconstitution may occur. The reconstituted solution should stand for 5 minutes. The solution should be colourless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. The solution must not be used if opaque particles, discolouration, or other foreign particles are present.

3. The required volume of the reconstituted Remsima solution should be diluted to 250 mL with sodium chloride 9 mg/mL (0.9%) solution for infusion. Do not dilute the reconstituted Remsima solution with any other diluent. The dilution can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250-mL glass bottle or infusion bag equal to the volume of reconstituted Remsima. The required volume of reconstituted Remsima solution should slowly be added to the 250-mL infusion bottle or bag and gently be mixed. For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL, 1000 mL) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/ mL. If stored refrigerated after reconstitution and dilution, the infusion solution must be allowed to equilibrate at room temperature to 25 °C for 3 hours prior to Step 4 (infusion). Storage beyond 24 hours at 2 °C - 8 °C applies to preparation of Remsima in the infusion bag only.

4. The infusion solution has to be administered over a period of not less than the infusion time recommended (see section 4.2). Only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometre or less) should be used. Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of reconstitution and dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution/dilution has been taken place in controlled and validated aseptic conditions (see section 6.3 above). Any unused portion of the infusion solution should not be stored for reuse.

5. Remsima should be visually inspected for particulate matter or discolouration prior to administration. If visibly opaque particles, discolouration or foreign particles are observed it should not be used.

6. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/001
EU/1/13/853/002
EU/1/13/853/003
EU/1/13/853/004
EU/1/13/853/005

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 September 2013
Date of latest renewal: 21 June 2018

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 120 mg solution for injection in pre-filled syringe
Remsima 120 mg solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Remsima 120 mg solution for injection in pre-filled syringe
Each 1 mL single dose pre-filled syringe contains 120 mg of infliximab*.

Remsima 120 mg solution for injection in pre-filled pen
Each 1 mL single dose pre-filled pen contains 120 mg of infliximab*.

* Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

Excipient(s) with known effect

This medicine contains 45 mg sorbitol (E420) and 0.5 mg polysorbate 80 (E433) in each mL of solution.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear to opalescent, colourless to pale brown solution.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Rheumatoid arthritis

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

Crohn's disease

Remsima is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Ulcerative colitis

Remsima is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis

Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
Remsima should be administered

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1).

Psoriasis

Remsima is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).

## 4.2 Posology and method of administration

Remsima treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima is indicated. Patients treated with Remsima should be given the package leaflet and the patient reminder card. Instruction for use is provided in the package leaflet.

For subsequent injections and after proper training in subcutaneous injection technique, patients may self-inject with Remsima if their physician determines that it is appropriate and with medical follow-up as necessary. Suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

During Remsima treatment, other concomitant therapies, e.g., corticosteroids and immunosuppressants should be optimised.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed. Remsima subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Posology

*Adults (≥18 years)*

*Rheumatoid arthritis*
Treatment with Remsima subcutaneous formulation should be initiated with loading doses of infliximab which may be intravenous or subcutaneous. When subcutaneous loading is used, Remsima 120 mg should be given as a subcutaneous injection followed by additional subcutaneous injections at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter. If intravenous loading doses of infliximab are given to initiate treatment, 2 intravenous infusions of infliximab 3 mg/kg should be given 2 weeks apart. The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the second intravenous administration. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

Remsima must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment (see section 5.1).

*Moderately to severely active Crohn's disease*
The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after loading doses of intravenous infliximab, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

Limited data in patients who initially responded to induction regimen with infliximab but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

*Fistulising, active Crohn's disease*
The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after loading doses of intravenous infliximab, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 14 weeks of the initial infusion.

Limited data in patients who initially responded to induction regimen with infliximab but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

*Ulcerative colitis*
The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

*Ankylosing spondylitis*
Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond by 6 weeks (i.e. after 2 intravenous infusions), no additional treatment with infliximab should be given.

*Psoriatic arthritis*
Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks.

*Psoriasis*
Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient shows no response after 14 weeks (i.e. 2 intravenous infusions and 5 subcutaneous injections), no additional treatment with infliximab should be given.

*Re-administration for Crohn's disease and rheumatoid arthritis*
From experience with intravenous infliximab, if the signs and symptoms of disease recur, infliximab can be re-administered within 16 weeks following the last administration. In clinical studies with intravenous infliximab, delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year (see sections 4.4 and 4.8). The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

*Re-administration for ulcerative colitis*
From experience with intravenous infliximab, the safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for ankylosing spondylitis*
From experience with intravenous infliximab, the safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for psoriatic arthritis*
From experience with intravenous infliximab, the safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for psoriasis*
Limited experience from re-treatment with one single intravenous infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen (see section 5.1).

Limited experience from re-treatment of intravenous infliximab following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment of intravenous infliximab (see section 4.8).

*Re-administration across indications*
In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen of intravenous infliximab is not recommended (see section 4.8). In this situation, infliximab should be re-initiated as a single dose of intravenous infliximab followed by the maintenance dose recommendations of subcutaneous infliximab described above given 4 weeks after the last administration of intravenous infliximab.

*Switching to and from Remsima subcutaneous formulation across indications*
When switching from the maintenance therapy of infliximab intravenous formulation to the subcutaneous formulation of Remsima, the subcutaneous formulation may be administered at the time of next planned administration of the intravenous infusions of infliximab.

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of Remsima.

Information regarding switching patients from the subcutaneous formulation to the intravenous formulation of Remsima is not available.

*Missed dose*

If patients miss an injection of Remsima subcutaneous formulation, they should be instructed to take the missed dose immediately in case this happens within 7 days from the missed dose, and then remain on their original dosing schedule. If the dose is delayed by 8 days or more, the patients should be instructed to skip the missed dose, wait until their next scheduled dose, and then remain on their original dosing schedule.

Special populations

*Elderly*

Specific studies of infliximab in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies with infliximab intravenous formulations and the same is expected for subcutaneous formulation. No dose adjustment is required (see section 5.2). For more information about the safety of infliximab in elderly patients (see sections 4.4 and 4.8).

*Renal and/or hepatic impairment*

Infliximab has not been studied in these patient populations. No dose recommendations can be made (see section 5.2).

*Paediatric population*

The safety and efficacy of Remsima subcutaneous therapy in children aged below 18 years of age have not yet been established. No data are available. Therefore, subcutaneous use of Remsima is recommended for use only in adults.

Method of administration

Remsima 120 mg solution for injection in pre-filled syringe or in pre-filled pen are administered by subcutaneous injection only. Full instructions for use are provided in the package leaflet. For the two initial intravenous infusions, patients may be pre-treated with, e.g., an antihistamine, hydrocortisone

and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously (see section 4.4). The physician should ensure appropriate follow-up of patients for any systemic injection reaction and localised injection site reaction after the initial subcutaneous injection is administered.

## 4.3 Contraindications

Hypersensitivity to the active substance, to other murine proteins or to any of the excipients listed in section 6.1.

Patients with tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections (see section 4.4).

Patients with moderate or severe heart failure (NYHA class III/IV) (see sections 4.4 and 4.8).

## 4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Systemic injection reaction/ localised injection site reaction/ hypersensitivity

Infliximab has been associated with systemic injection reactions, anaphylactic shock and delayed hypersensitivity reactions (see section 4.8).

Acute reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following administration of infliximab. If acute reactions occur, medical treatment should be sought immediately. For this reason, the initial intravenous administrations should take place where emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway is immediately available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Localised injection site reactions predominantly of mild to moderate in nature included the following reactions limited to injection site: erythema, pain, pruritus, swelling, induration, bruising, haematoma, oedema, coldness, paraesthesia, haemorrhage, irritation, rash, ulcer, urticaria, application site vesicles and scab were reported to be associated with infliximab subcutaneous treatment. Most of these reactions may occur immediately or within 24 hours after subcutaneous injection. Most of these reactions resolved spontaneously without any treatment.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions when administered by intravenous infusion. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed with intravenously administered infliximab. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and in the case of intravenously administered infliximab, a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically-treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab must not be administered (see section 4.8).

In clinical studies, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab free interval. Patients should be advised to seek immediate medical advice if they experience any delayed adverse reaction (see section

4.8). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with infliximab. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with infliximab must not be given if a patient develops a serious infection or sepsis.

Caution should be exercised when considering the use of infliximab in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Tumour necrosis factor alpha (TNFα) mediates inflammation and modulates cellular immune responses. Experimental data show that TNFα is essential for the clearing of intracellular infections. Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab.

It should be noted that suppression of TNFα may mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections and of typical clinical presentation of rare and unusual infections is critical in order to minimise delays in diagnosis and treatment.

Patients taking TNF-blockers are more susceptible to serious infections.

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis.

Patients who develop a new infection while undergoing treatment with infliximab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

*Tuberculosis*

There have been reports of active tuberculosis in patients receiving infliximab. It should be noted that in the majority of these reports tuberculosis was extrapulmonary, presenting as either local or disseminated disease.

Before starting treatment with infliximab, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, (e.g. tuberculin skin test, chest X-ray, and/or Interferon Gamma Release Assay), should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient reminder card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, infliximab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of infliximab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with antituberculosis therapy before the initiation of infliximab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, antituberculosis therapy should be considered before the initiation of infliximab.

Use of antituberculosis therapy should also be considered before the initiation of infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Some cases of active tuberculosis have been reported in patients treated with infliximab during and after treatment for latent tuberculosis.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after infliximab treatment.

*Invasive fungal infections*

In patients treated with infliximab, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness, and a physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients.

Invasive fungal infections may present as disseminated rather than localised disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of infliximab treatment should be carefully considered before initiation of infliximab therapy.

*Fistulising Crohn's disease*
Patients with fistulising Crohn's disease with acute suppurative fistulas must not initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded (see section 4.3).

Hepatitis B (HBV) reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with infliximab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with infliximab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with antiviral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, infliximab should be stopped and effective antiviral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. Patients with symptoms or signs of liver dysfunction

should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥5 times the upper limit of normal develop(s), infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent administration of TNF-alpha inhibitor and anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of infliximab and anakinra is not recommended.

Concurrent administration of TNF-alpha inhibitor and abatacept

In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of infliximab and abatacept is not recommended.

Concurrent administration with other biological therapeutics

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs

Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse reactions, including infection.

Vaccinations

It is recommended that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

In a subset of 90 adult patients with rheumatoid arthritis from the ASPIRE study a similar proportion of patients in each treatment group (methotrexate plus: placebo [n = 17], 3 mg/kg [n = 27] or 6 mg/kg infliximab [n = 46]) mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine, indicating that infliximab did not interfere with T-cell independent humoral immune responses. However, studies from the published literature in various indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) suggest that non-live vaccinations received during treatment with anti-TNF therapies, including infliximab may elicit a lower immune response than in patients not receiving anti-TNF therapy.

Live vaccines/therapeutic infectious agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with infliximab is not recommended.

Infant exposure *in utero*

In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. A twelve

month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see section 4.6).

Infant exposure via breast milk
Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see section 4.6).

Therapeutic infectious agents

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with infliximab.

Autoimmune processes

The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab and is positive for antibodies against double-stranded DNA, further treatment with infliximab must not be given (see section 4.8).

Neurological events

Use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical studies of infliximab across all approved indications the incidence of lymphoma in infliximab-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

In an exploratory clinical study evaluating the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Caution should be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking.

With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded (see section 4.8). Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.

Although subcutaneous administration is not indicated for children under age of 18 years, it should be noted that malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.8).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. Periodic screening should continue in women treated with infliximab, including those over 60 years of age.

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that infliximab treatment influences the risk for developing dysplasia or colon cancer.

Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits of continued therapy to the individual patients should be carefully considered by the clinician.

Heart failure

Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure (see sections 4.3 and 4.8).

Haematologic reactions

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of infliximab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Others

There is limited safety experience of infliximab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life of infliximab should be taken into consideration

if a surgical procedure is planned. A patient who requires surgery while on infliximab should be closely monitored for infections, and appropriate actions should be taken.

Failure to respond to treatment for Crohn's disease may indicate the presence of a fixed fibrotic stricture that may require surgical treatment. There is no evidence to suggest that infliximab worsens or causes fibrotic strictures.

Special populations

*Elderly*

The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly (see section 4.8).

Excipients with known effect

*Sodium and sorbitol contents*

Remsima contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free' and 45 mg sorbitol per 1 mL (in each 120 mg dose).

*Polysorbate 80*

This medicine contains 0.5 mg of polysorbate 80 in each pre-filled syringe/pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.

Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent.

The combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended (see section 4.4).

It is recommended that live vaccines not be given concurrently with Remsima. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for 12 months following birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see section 4.4).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see sections 4.4 and 4.6).

It is recommended that therapeutic infectious agents not be given concurrently with infliximab (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Pregnancy

The moderate number of prospectively collected pregnancies exposed to infliximab resulting in live birth with known outcomes, including approximately 1,100 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

Based on an observational study from Northern Europe, an increased risk (OR, 95% CI; p-value) for C-section (1.50, 1.14-1.96; p = 0.0032), preterm birth (1.48, 1.05-2.09; p = 0.024), small for gestational age (2.79, 1.54-5.04; p = 0.0007), and low birth weight (2.03, 1.41-2.94; p = 0.0002) was observed in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids, 270 pregnancies) as compared to women exposed to immunomodulators and/or corticosteroids only (6,460 pregnancies). The potential contribution of exposure to infliximab and/or the severity of the underlying disease in these outcomes remains unclear.

Due to its inhibition of TNFα, infliximab administered during pregnancy could affect normal immune responses in the newborn. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity (see section 5.3).

The available clinical experience is limited. Infliximab should only be used during pregnancy if clearly needed.

Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth (see sections 4.4 and 4.5). If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. Cases of agranulocytosis have also been reported (see section 4.8).

Breast-feeding

Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding.

Fertility

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Remsima may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of infliximab (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials with infliximab, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for infliximab include HBV reactivation, CHF (congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease) and serious infusion reactions (see section 4.4).

The safety profile of Remsima subcutaneous formulation from active rheumatoid arthritis (evaluated in 168 and 175 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively), active Crohn's disease (evaluated in 297, 38 and 105 patients for the subcutaneous infliximab group, the intravenous infliximab group and the placebo group, respectively) and active ulcerative colitis patients (evaluated in 334, 40 and 140 patients for the subcutaneous infliximab group, the intravenous infliximab group and the placebo group, respectively) was overall similar to the safety profile of the intravenous formulation.

Tabulated list of adverse reactions

Table 1 lists the ADRs based on experience from clinical studies as well as adverse reactions, some with fatal outcome, reported from post-marketing experience. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1**
**Adverse reactions in clinical studies and from post-marketing experience of infliximab**

| | |
|---|---|
| *Infections and infestations* | |
| Very common: | Viral infection (e.g. influenza, herpes virus infection, COVID-19*). |
| Common: | Bacterial infections (e.g. sepsis, cellulitis, abscess). |
| Uncommon: | Tuberculosis, fungal infections (e.g. candidiasis, onychomycosis). |
| Rare: | Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation. |
| Not known: | Vaccine breakthrough infection (after *in utero* exposure to infliximab)**. |
| *Neoplasms benign, malignant and unspecified (including cysts and polyps)* | |
| Rare: | Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer. |
| Not known: | Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease and ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma. |

| | |
|---|---|
| *Blood and lymphatic system disorders* | |
| Common: | Neutropenia, leukopenia, anaemia, lymphadenopathy. |
| Uncommon: | Thrombocytopenia, lymphopenia, lymphocytosis. |
| Rare: | Agranulocytosis (including infants exposed *in utero* to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura. |
| *Immune system disorders* | |
| Common: | Allergic respiratory symptom. |
| Uncommon: | Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction. |
| Rare | Anaphylactic shock, vasculitis, sarcoid-like reaction |
| *Metabolism and nutrition disorders* | |
| Uncommon: | Dyslipidaemia. |
| *Psychiatric disorders* | |
| Common: | Depression, insomnia. |
| Uncommon: | Amnesia, agitation, confusion, somnolence, nervousness. |
| Rare: | Apathy. |
| *Nervous system disorders* | |
| Very common: | Headache. |
| Common: | Vertigo, dizziness, hypoaesthesia, paraesthesia. |
| Uncommon: | Seizure, neuropathy. |
| Rare: | Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy). |
| Not known: | Cerebrovascular accidents in close temporal association with infusion. |
| *Eye disorders* | |
| Common | Conjunctivitis |
| Uncommon | Keratitis, periorbital oedema, hordeolum |
| Rare | Endophthalmitis |
| Not known | Transient visual loss occurring during or within 2 hours of infusion |
| *Cardiac disorders* | |
| Common | Tachycardia, palpitation |
| Uncommon | Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia |
| Rare | Cyanosis, pericardial effusion |
| Not known | Myocardial ischaemia/myocardial infarction |
| *Vascular disorders* | |
| Common | Hypotension, hypertension, ecchymosis, hot flush, flushing |
| Uncommon | Peripheral ischaemia, thrombophlebitis, haematoma |
| Rare | Circulatory failure, petechia, vasospasm |
| *Respiratory, thoracic and mediastinal disorders* | |
| Very common | Upper respiratory tract infection, sinusitis |
| Common | Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis |
| Uncommon | Pulmonary oedema, bronchospasm, pleurisy, pleural effusion |
| Rare | Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis) |

| | | |
|---|---|---|
| *Gastrointestinal disorders* | | |
| | Very common: | Abdominal pain, nausea |
| | Common: | Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation |
| | Uncommon | Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis |
| *Hepatobiliary disorders* | | |
| | Common: | Hepatic function abnormal, transaminases increased. |
| | Uncommon: | Hepatitis, hepatocellular damage, cholecystitis. |
| | Rare: | Autoimmune hepatitis, jaundice. |
| | Not known: | Liver failure. |
| *Skin and subcutaneous tissue disorders* | | |
| | Common: | New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia. |
| | Uncommon: | Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation. |
| | Rare: | Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions. |
| | Not known: | Worsening of symptoms of dermatomyositis. |
| *Musculoskeletal and connective tissue disorders* | | |
| | Common: | Arthralgia, myalgia, back pain. |
| *Renal and urinary disorders* | | |
| | Common: | Urinary tract infection. |
| | Uncommon: | Pyelonephritis. |
| *Reproductive system and breast disorders* | | |
| | Uncommon: | Vaginitis. |
| *General disorders and administration site conditions* | | |
| | Very common: | Infusion-related reaction, pain. |
| | Common: | Chest pain, fatigue, fever, injection site reaction, chills, oedema. |
| | Uncommon: | Impaired healing. |
| | Rare: | Granulomatous lesion. |
| *Investigations* | | |
| | Uncommon: | Autoantibody positive, weight increased[1]. |
| | Rare: | Complement factor abnormal. |

* COVID-19 was seen with the SC administered Remsima

** including bovine tuberculosis (disseminated BCG infection), see section 4.4

[1] At month 12 of the controlled period for adult clinical trials across all indications, the median weight increase was 3.50 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects. The median weight increase for inflammatory bowel disease indications was 4.14 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects, and the median weight increase for rheumatology indications was 3.40 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects.

Description of selected adverse drug reactions

*Systemic injection reaction and localised injection site reaction in adult patients administered with Remsima subcutaneous formulation*

The safety profile of Remsima subcutaneous formulation in combination with methotrexate was evaluated in a Phase I/III parallel group study in patients with active rheumatoid arthritis. The safety population consisted of 168 patients in the Remsima subcutaneous group and 175 patients in the Remsima intravenous group. For study details, see Section 5.1.

The incidence rate of systemic injection reactions (e.g. rash, pruritus, flushing and oedema) was 1.2 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 2.1 patients per 100 patient-years in the Remsima intravenous group who switched to Remsima subcutaneous administration (from Week 30). All systemic injection reactions were mild to moderate.

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus and swelling) was 17.6 patients per 100 patient-years in the Remsima subcutaneous group (from Week 6) and 21.4 patients per 100 patient-years in those who switched to Remsima subcutaneous administration (from Week 30). Most of these reactions were mild to moderate and resolved spontaneously without any treatment within a day.

In the integrated analysis including a Phase I study conducted in patients with active Crohn's disease and active ulcerative colitis, a Phase III study conducted in patients with active Crohn's disease and a Phase III study conducted in patients with active ulcerative colitis, the safety population consisted of 631 patients in the Remsima subcutaneous group (297 patients with active Crohn's disease and 334 patients with active ulcerative colitis) and 245 patients in the Placebo group (105 patients with active Crohn's disease and 140 patients with active ulcerative colitis). For study details, see Section 5.1.

The incidence rate of systemic injection reactions (e.g. nausea and dizziness) was 3.56 patients per 100 patient-years in the Remsima subcutaneous group.

The incidence rate of localised injection site reactions (e.g. injection site erythema, pain, pruritus, bruising) was 8.68 patients per 100 patient-years in the Remsima subcutaneous group. Most of these reactions were mild to moderate and mostly resolved spontaneously without any treatment within a few days.

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with infliximab intravenous administration (see section 4.4). Cases of transient visual loss occurring during or within 2 hours of infliximab infusion have been reported. Events (some fatal) of myocardial ischaemia/infarction and arrhythmia have been reported, some in close temporal association with infusion of infliximab; cerebrovascular accidents have also been reported in close temporal association with infusion of infliximab.

*Delayed hypersensitivity*

In clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year. In the psoriasis studies with intravenous infliximab, delayed hypersensitivity reactions occurred early in the treatment course. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients experiencing pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache.

There are insufficient data on the incidence of delayed hypersensitivity reactions after infliximab-free intervals of more than 1 year but limited data from clinical studies suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval (see section 4.4).

In a 1-year clinical study with repeated infusions of IV infliximab in patients with Crohn's disease (ACCENT I study), the incidence of serum sickness-like reactions was 2.4%.

*Immunogenicity*

*Intravenous formulation*

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion-related reactions.
In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 14% of patients with any immunosuppressant therapy, and in 24% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 8% of patients developed antibodies to infliximab. In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15% of patients (antibodies occurred in 4% of patients receiving methotrexate and in 26% of patients not receiving methotrexate at baseline). In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab (see section 4.4: "Systemic injection reaction/ localised injection site reaction/ hypersensitivity").

Because immunogenicity analyses are assay-specific, comparison of the incidence of antibodies to infliximab reported in this section with the incidence of antibodies in other studies may be misleading.

*Subcutaneous formulation*

In rheumatoid arthritis patients on maintenance treatment, the incidence of anti-infliximab antibodies following the subcutaneous infliximab was demonstrated to be not higher than that of the intravenous infliximab and anti-infliximab antibodies had no significant impact on efficacy (determined by disease activity score in 28 joints [DAS28] and American College of Rheumatology criteria 20 [ACR20]) and the safety profile.

In Crohn's disease and ulcerative colitis patients on maintenance treatment, the incidence of anti-infliximab antibodies was not higher in patients who received subcutaneous infliximab in comparison to those who received intravenous infliximab. In Crohn’s disease and ulcerative colitis patients, there was a correlation between loss of response and anti-infliximab antibodies, while anti-infliximab antibodies had no significant impact on the safety profile.

*Infections*

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis (see section 4.4).

In clinical studies 36% of infliximab-treated patients were treated for infections compared with 25% of placebo-treated patients.

In rheumatoid arthritis clinical studies, the incidence of serious infections including pneumonia was higher in infliximab plus methotrexate-treated patients compared with methotrexate alone especially at doses of 6 mg/kg or greater (see section 4.4).

In post-marketing spontaneous reporting, infections are the most common serious adverse reaction. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been

associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported (see section 4.4).

*Malignancies and lymphoproliferative disorders*

In clinical studies with infliximab in which 5,780 patients were treated, representing 5,494 patient years, 5 cases of lymphomas and 26 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1,600 placebo-treated patients representing 941 patient years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6,234 patients-years (3,210 patients), 5 cases of lymphoma and 38 cases of non-lymphoma malignancies were reported.

Cases of malignancies, including lymphoma, have also been reported in the post-marketing setting (see section 4.4).

In an exploratory clinical study involving patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 adult patients were treated with infliximab at doses similar to those used in rheumatoid arthritis and Crohn's disease. Nine of these patients developed malignancies, including 1 lymphoma. The median duration of follow-up was 0.8 years (incidence 5.7% [95% CI 2.65%-10.6%]. There was one reported malignancy amongst 77 control patients (median duration of follow-up 0.8 years; incidence 1.3% [95% CI 0.03%-7.0%]). The majority of the malignancies developed in the lung or head and neck.

A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age (see section 4.4).

In addition, post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with infliximab with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, and most of whom were adolescent or young adult males (see section 4.4).

*Heart failure*

In a Phase II study aimed at evaluating infliximab in CHF, higher incidence of mortality due to worsening of heart failure were seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this study 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction ≤35%) were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

*Hepatobiliary events*

In clinical studies, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT ≥5 x Upper Limit of Normal (ULN) have been observed (see Table 2). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed

ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant therapy. In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4).

**Table 2**
**Proportion of patients with increased ALT activity in clinical studies using intravenous infliximab**

| Indication | Number of patients[3] | | Median follow-up (wks)[4] | | ≥ 3 x ULN | | ≥ 5 x ULN | |
|---|---|---|---|---|---|---|---|---|
| | placebo | infliximab | placebo | infliximab | placebo | infliximab | placebo | infliximab |
| Rheumatoid arthritis[1] | 375 | 1,087 | 58.1 | 58.3 | 3.2% | 3.9% | 0.8% | 0.9% |
| Crohn's disease[2] | 324 | 1,034 | 53.7 | 54.0 | 2.2% | 4.9% | 0.0% | 1.5% |
| Ulcerative colitis | 242 | 482 | 30.1 | 30.8 | 1.2% | 2.5% | 0.4% | 0.6% |
| Ankylosing spondylitis | 76 | 275 | 24.1 | 101.9 | 0.0% | 9.5% | 0.0% | 3.6% |
| Psoriatic arthritis | 98 | 191 | 18.1 | 39.1 | 0.0% | 6.8% | 0.0% | 2.1% |
| Plaque psoriasis | 281 | 1,175 | 16.1 | 50.1 | 0.4% | 7.7% | 0.0% | 3.4% |

1 Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
2 Placebo patients in the 2 Phase III studies in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomised to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day as active control in addition to placebo infliximab infusions.
3 Number of patients evaluated for ALT.
4 Median follow-up is based on patients treated.

*Antinuclear antibodies (ANA)/Anti-double-stranded DNA (dsDNA) antibodies*

Approximately half of infliximab-treated patients in clinical studies who were ANA negative at baseline developed a positive ANA during the study compared with approximately one fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of infliximab-treated patients compared with 0% of placebo-treated patients. At the last evaluation, 57% of infliximab-treated patients remained anti-dsDNA positive. Reports of lupus and lupus-like syndromes, however, remain uncommon (see section 4.4).

Other special populations

*Elderly*

In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in infliximab plus methotrexate-treated patients 65 years and older (11.3%) than in those under 65 years of age (4.6%). In patients treated with methotrexate alone, the incidence of serious infections was 5.2% in patients 65 years and older compared to 2.7% in patients under 65 (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Single intravenous doses up to 20 mg/kg have been administered without toxic effects and repeated doses of Remsima subcutaneous formulation up to 240 mg have been administered without toxic effects. There is no specific treatment for Remsima overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, tumour necrosis factor alpha (TNFα) inhibitors, ATC code: L04AB02

Remsima is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Mechanism of action

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα but not to lymphotoxin α (TNFβ).

Pharmacodynamic effects

Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity.

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP), and increased haemoglobin levels in rheumatoid arthritis patients with reduced haemoglobin levels, compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalisation of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, short term treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin.

Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable $TNF_{\alpha}$. Infliximab treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, CRP. Total peripheral white blood cell counts were minimally affected in infliximab-treated patients, although changes in lymphocytes, monocytes and neutrophils reflected shifts towards normal ranges. Peripheral blood mononuclear cells (PBMC) from infliximab-treated patients showed undiminished proliferative responsiveness to stimuli compared with untreated patients, and no substantial changes in cytokine production by stimulated PBMC were observed following treatment with infliximab. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that infliximab treatment caused a reduction in the number of cells capable of expressing $TNF_{\alpha}$ and interferon γ. Additional histological studies provided evidence that treatment with infliximab reduces the infiltration of inflammatory cells into affected areas of the

intestine and the presence of inflammation markers at these sites. Endoscopic studies of intestinal mucosa have shown evidence of mucosal healing in infliximab-treated patients.

Clinical efficacy and safety

*Adult rheumatoid arthritis*

*Intravenous formulation*

The efficacy of infliximab intravenous formulation was assessed in two multicentre, randomised, double-blind, pivotal clinical studies: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the ACR criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of the following 5 criteria: (1) evaluator's global assessment, (2) patient's global assessment, (3) functional/disability measure, (4) visual analogue pain scale and (5) erythrocyte sedimentation rate or C-reactive protein. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percent improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function.

The ATTRACT study evaluated responses at 30, 54 and 102 weeks in a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter. All patients were on stable methotrexate doses (median 15 mg/wk) for 6 months prior to enrolment and were to remain on stable doses throughout the study.

Results from week 54 (ACR20, total van der Heijde-modified Sharp score and HAQ) are shown in Table 3. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 3).

The effects observed at 54 weeks were maintained through 102 weeks. Due to a number of treatment withdrawals, the magnitude of the effect difference between infliximab and the methotrexate alone group cannot be defined.

**Table 3**
**Effects on ACR20, Structural Joint Damage and Physical Function at week 54, ATTRACT**

| | | Infliximab[b] | | | | |
|---|---|---|---|---|---|---|
| | Control[a] | 3 mg/kg q 8 wks | 3 mg/kg q 4 wks | 10 mg/kg q 8 wks | 10 mg/kg q 4 wks | All infliximab[b] |
| Patients with ACR20 response/Patients evaluated (%) | 15/88 (17%) | 36/86 (42%) | 41/86 (48%) | 51/87 (59%) | 48/81 (59%) | 176/340 (52%) |
| Total score[d] (van der Heijde-modified Sharp score) | | | | | | |
| Change from baseline (Mean ± SD[c]) | 7.0 ± 10.3 | 1.3 ± 6.0 | 1.6 ± 8.5 | 0.2 ± 3.6 | -0.7 ± 3.8 | 0.6 ± 5.9 |
| Median | 4.0 | 0.5 | 0.1 | 0.5 | -0.5 | 0.0 |

| | Control[a] | Infliximab[b] | | | | |
|---|---|---|---|---|---|---|
| | | 3 mg/kg q 8 wks | 3 mg/kg q 4 wks | 10 mg/kg q 8 wks | 10 mg/kg q 4 wks | All infliximab[b] |
| (Interquartile range) | (0.5,9.7) | (-1.5,3.0) | (-2.5,3.0) | (-1.5,2.0) | (-3.0,1.5) | (-1.8,2.0) |
| Patients with no deterioration/patients evaluated (%)[c] | 13/64 (20%) | 34/71 (48%) | 35/71 (49%) | 37/77 (48%) | 44/66 (67%) | 150/285 (53%) |
| HAQ change from baseline over time[e] (patients evaluated) | 87 | 86 | 85 | 87 | 81 | 339 |
| Mean ± SD[c] | 0.2 ± 0.3 | 0.4 ± 0.3 | 0.5 ± 0.4 | 0.5 ± 0.5 | 0.4 ± 0.4 | 0.4 ± 0.4 |

a control = All patients had active RA despite treatment with stable methotrexate doses for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤10 mg/day) and/or NSAIDs was permitted, and folate supplementation was given.
b all infliximab doses given in combination with methotrexate and folate with some on corticosteroids and/or NSAIDs
c p <0.001, for each infliximab treatment group vs. control
d greater values indicate more joint damage.
e HAQ = Health Assessment Questionnaire; greater values indicate less disability.

The ASPIRE study evaluated responses at 54 weeks in 1,004 methotrexate naive patients with early (≤3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (optimised to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from week 54 are shown in Table 4.

After 54 weeks of treatment, both doses of infliximab + methotrexate resulted in statistically significantly greater improvement in signs and symptoms compared to methotrexate alone as measured by the proportion of patients achieving ACR20, 50 and 70 responses.

In ASPIRE, more than 90% of patients had at least two evaluable X-rays. Reduction in the rate of progression of structural damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone.

**Table 4**
**Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE**

| | | Infliximab + MTX | | |
|---|---|---|---|---|
| | Placebo + MTX | 3 mg/kg | 6 mg/kg | Combined |
| Subjects randomised | 282 | 359 | 363 | 722 |
| Percentage ACR improvement | | | | |
| Mean ± SD[a] | 24.8 ± 59.7 | 37.3 ± 52.8 | 42.0 ± 47.3 | 39.6 ± 50.1 |
| Change from baseline in total van der Heijde-modified Sharp score[b] | | | | |
| Mean ± SD[a] | 3.70 ± 9.61 | 0.42 ± 5.82 | 0.51 ± 5.55 | 0.46 ± 5.68 |
| Median | 0.43 | 0.00 | 0.00 | 0.00 |
| Improvement from baseline in HAQ averaged over time from week 30 to week 54[c] | | | | |
| Mean ± SD[d] | 0.68 ± 0.63 | 0.80 ± 0.65 | 0.88 ± 0.65 | 0.84 ± 0.65 |

a p <0.001, for each infliximab treatment group vs control.
b greater values indicate more joint damage.
c HAQ = Health Assessment Questionnaire; greater values indicate less disability.
d p = 0.030 and <0.001 for the 3 mg/kg and 6 mg/kg treatment groups respectively vs. placebo + MTX.

Data to support dose titration in rheumatoid arthritis come from ATTRACT, ASPIRE and the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the study arms (group 2, n=329), patients with an inadequate response were allowed to dose titrate with 1.5 mg/kg increments from 3 up to 9 mg/kg. The majority (67%) of these patients did not require any dose titration. Of the patients who required a dose titration, 80% achieved clinical response and the majority (64%) of these required only one adjustment of 1.5 mg/kg.

*Subcutaneous formulation*

The efficacy of subcutaneous infliximab in rheumatoid arthritis patients was assessed in a randomised, parallel-group pivotal Phase I/III study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of efficacy of subcutaneous infliximab compared to intravenous infliximab treatment in a double-blind setting.

In Part 2 of this study, among 357 patients who were enrolled to receive 2 doses of Remsima 3 mg/kg intravenously at Weeks 0 and 2, 167 patients were randomised to receive Remsima 120 mg subcutaneously at Week 6 and every 2 weeks up to Week 54, while 176 patients were randomised to receive Remsima 3 mg/kg intravenously at Weeks 6, 14 and 22 and then switched to Remsima 120 mg subcutaneous at Week 30 once-every 2 weeks up to Week 54. Methotrexate was given concomitantly.

The primary endpoint of the study was the treatment difference of the change from baseline of DAS28 (CRP) at Week 22. The estimate of treatment difference was 0.27 with corresponding lower limit of the two-sided 95% confidence interval [CI] of 0.02 (95% CI: 0.02, 0.52), which was greater than the pre-specified non-inferiority margin of -0.6 indicating non-inferiority of Remsima subcutaneous formulation to Remsima intravenous formulation.

The analysis of other efficacy endpoints showed that efficacy profile of Remsima subcutaneous formulation compared to Remsima intravenous formulation in RA patients was generally comparable in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to Week 54. The mean scores for DAS28 (CRP) and DAS28 (ESR) gradually decreased from baseline at each time point until Week 54 in each treatment arm (see Table 5 and Table 6, respectively).

**Table 5**
**Mean (SD) Actual Values of DAS28 (CRP and ESR)**

| | **DAS28 (CRP)** | | **DAS28 (ESR)** | |
|---|---|---|---|---|
| **Visit** | **Remsima IV 3 mg/kg[b] (N=174)** | **Remsima SC 120 mg (N=165)** | **Remsima IV 3 mg/kg[b] (N=174)** | **Remsima SC 120 mg (N=165)** |
| **Baseline** | 5.9 (0.8) | 6.0 (0.8) | 6.6 (0.8) | 6.7 (0.8) |
| **Week 6** | 4.1 (1.2) | 4.0 (1.2) | 4.8 (1.3) | 4.6 (1.2) |
| **Week 22** | 3.5 (1.2)[a] | 3.3 (1.1)[a] | 4.1 (1.3) | 4.0 (1.1) |
| **Week 54** | 2.9 (1.2)[b] | 2.8 (1.1) | 3.4 (1.3)[b] | 3.4 (1.2) |

a Two-sided 95% CI for difference in the mean change from baseline for DAS28 (CRP) at Week 22 was well above the pre-defined non-inferiority margin of -0.6
b Remsima IV was switched to Remsima SC at Week 30

**Table 6**
**Proportions of Patients Achieving Clinical Response According to the ACR Criteria**

| | **ACR20** | | **ACR50** | | **ACR70** | |
|---|---|---|---|---|---|---|
| **Visit** | **Remsima IV 3 mg/kg[a] (N=174)** | **Remsima SC 120 mg (N=165)** | **Remsima IV 3 mg/kg[a] (N=174)** | **Remsima SC 120 mg (N=165)** | **Remsima IV 3 mg/kg[a] (N=174)** | **Remsima SC 120 mg (N=165)** |
| **Week 6** | 103 (59.2%) | 107 (64.8%) | 45 (25.9%) | 47 (28.5%) | 18 (10.3%) | 19 (11.5%) |
| **Week 22** | 137 (78.7%) | 139 (84.2%) | 90 (51.7%) | 85 (51.5%) | 49 (28.2%) | 46 (27.9%) |
| **Week 54** | 125 (71.8%)[a] | 132 (80.0%) | 101 (58.0%)[a] | 108 (65.5%) | 68 (39.1%)[a] | 77 (46.7%) |

a Remsima IV was switched to Remsima SC at Week 30

There are no clinical trials with Remsima 120 mg given subcutaneously without intravenous loading doses of infliximab in patients with rheumatoid arthritis. However, population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable infliximab exposure (AUC over 8 weeks) and efficacy (DAS28 and ACR20 response) from Week 6 onward in rheumatoid arthritis patients treated with Remsima 120 mg given without intravenous loading doses of infliximab when compared with Remsima 3 mg/kg given intravenously at Weeks 0, 2 and 6, and then every 8 weeks.

*Adult Crohn's disease*

*Intravenous formulation*

*Induction treatment in moderately to severely active Crohn's disease*
The efficacy of a single dose treatment with infliximab intravenous formulation was assessed in 108 patients with active Crohn's disease (CDAI ≥220 ≤400) in a randomised, double-blinded, placebo-controlled, dose-response study. Of these 108 patients, 27 were treated with the recommended dosage of infliximab 5 mg/kg. All patients had experienced an inadequate response to prior conventional therapies. Concurrent use of stable doses of conventional therapies was permitted, and 92% of patients continued to receive these therapies.

The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥70 points from baseline at the 4-week evaluation and without an increase in the use of medicinal products or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients in clinical remission at week 4 (CDAI <150) and clinical response over time.

At week 4, following administration of a single dose, 22/27 (81%) of infliximab-treated patients receiving a 5 mg/kg dose achieved a clinical response vs. 4/25 (16%) of the placebo-treated patients ($p < 0.001$). Also at week 4, 13/27 (48%) of infliximab-treated patients achieved a clinical remission (CDAI <150) vs. 1/25 (4%) of placebo-treated patients. A response was observed within 2 weeks, with a maximum response at 4 weeks. At the last observation at 12 weeks, 13/27 (48%) of infliximab-treated patients were still responding.

*Maintenance treatment in moderately to severely active Crohn's disease in adults*
The efficacy of repeated infusions with intravenous infliximab was studied in a 1-year clinical study (ACCENT I). A total of 573 patients with moderately to severely active Crohn's disease (CDAI ≥220 ≤400) received a single infusion of 5 mg/kg at week 0. 178 of the 580 enrolled patients (30.7%) were defined as having severe disease (CDAI score > 300 and concomitant corticosteroid and/or immunosuppressants) corresponding to the population defined in the indication (see section 4.1). At week 2, all patients were assessed for clinical response and randomised to one of 3 treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group. All 3 groups received repeated infusions at week 2, 6 and every 8 weeks thereafter.

Of the 573 patients randomised, 335 (58%) achieved clinical response by week 2. These patients were classified as week-2 responders and were included in the primary analysis (see Table 7). Among patients classified as non-responders at week 2, 32% (26/81) in the placebo maintenance group and 42% (68/163) in the infliximab group achieved clinical response by week 6. There was no difference between groups in the number of late responders thereafter.

The co-primary endpoints were the proportion of patients in clinical remission (CDAI <150) at week 30 and time to loss of response through week 54. Corticosteroid tapering was permitted after week 6.

**Table 7**
**Effects on response and remission rate, data from ACCENT I (Week-2 responders)**

| | ACCENT I (Week-2 responders) % of patients | | |
|---|---|---|---|
| | Placebo Maintenance (n=110) | Infliximab Maintenance 5 mg/kg (n=113) (p value) | Infliximab Maintenance 10 mg/kg (n=112) (p value) |
| Median time to loss of response through week 54 | 19 weeks | 38 weeks (0.002) | >54 weeks (<0.001) |
| **Week 30** | | | |
| Clinical Response[a] | 27.3 | 51.3 (<0.001) | 59.1 (<0.001) |
| Clinical Remission | 20.9 | 38.9 (0.003) | 45.5 (<0.001) |
| Steroid-Free Remission | 10.7 (6/56) | 31.0 (18/58) (0.008) | 36.8 (21/57) (0.001) |
| **Week 54** | | | |
| Clinical Response[a] | 15.5 | 38.1 (<0.001) | 47.7 (<0.001) |
| Clinical Remission | 13.6 | 28.3 (0.007) | 38.4 (<0.001) |
| Sustained Steroid-Free Remission[b] | 5.7 (3/53) | 17.9 (10/56) (0.075) | 28.6 (16/56) (0.002) |

a Reduction in CDAI ≥25% and ≥70 points.
b CDAI <150 at both Week 30 and 54 and not receiving corticosteroids in the 3 months prior to Week 54 among patients who were receiving corticosteroids at baseline.

Beginning at week 14, patients who had responded to treatment, but subsequently lost their clinical benefit, were allowed to cross over to a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Eighty nine percent (50/56) of patients who lost clinical response on infliximab 5 mg/kg maintenance therapy after week 14 responded to treatment with infliximab 10 mg/kg.

Improvements in quality of life measures, a reduction in disease-related hospitalisations and corticosteroid use were seen in the infliximab maintenance groups compared with the placebo maintenance group at weeks 30 and 54.

Infliximab with or without AZA was assessed in a randomised, double-blind, active comparator study (SONIC) of 508 adult patients with moderate to severe Crohn's disease (CDAI ≥220 ≤450) who were naive to biologics and immunosuppressants and had a median disease duration of 2.3 years. At baseline 27.4% of patients were receiving systemic corticosteroids, 14.2% of patients were receiving budesonide, and 54.3% of patients were receiving 5-ASA compounds. Patients were randomised to receive AZA monotherapy, infliximab monotherapy, or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily.

The primary endpoint of the study was corticosteroid-free clinical remission at week 26, defined as patients in clinical remission (CDAI of <150) who, for at least 3 weeks, had not taken oral systemic corticosteroids (prednisone or equivalent) or budesonide at a dose >6 mg/day. For results see Table 8. The proportions of patients with mucosal healing at week 26 were significantly greater in the infliximab plus AZA combination (43.9%, p<0.001) and infliximab monotherapy groups (30.1%, p=0.023) compared to the AZA monotherapy group (16.5%).

**Table 8**
**Percent of patients achieving corticosteroid-free clinical remission at Week 26, SONIC**

| | AZA Monotherapy | Infliximab Monotherapy | Infliximab + AZA Combination therapy |
|---|---|---|---|
| **Week 26** | | | |
| All randomised patients | 30.0% (51/170) | 44.4% (75/169) (p=0.006)* | 56.8% (96/169) (p<0.001)* |

* p-values represent each infliximab treatment group vs. AZA monotherapy.

Similar trends in the achievement of corticosteroid-free clinical remission were observed at week 50. Furthermore, improved quality of life as measured by IBDQ was observed with infliximab.

*Induction treatment in fistulising active Crohn's disease*
The efficacy was assessed in a randomised, double-blinded, placebo-controlled study in 94 patients with fistulising Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty one of these patients were treated with infliximab intravenous formulation 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these therapies. Patients received three doses of either placebo or infliximab at weeks 0, 2 and 6. Patients were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistulae draining upon gentle compression on at least two consecutive visits (4 weeks apart), without an increase in the use of medicinal products or surgery for Crohn's disease.

Sixty eight percent (21/31) of infliximab-treated patients receiving a 5 mg/kg dose regimen achieved a clinical response vs. 26% (8/31) placebo-treated patients (p=0.002). The median time to onset of response in the infliximab-treated group was 2 weeks. The median duration of response was 12 weeks. Additionally, closure of all fistulae was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients (p=0.001).

*Maintenance treatment in fistulising active Crohn's disease*
The efficacy of repeated infusions with infliximab in patients with fistulising Crohn's disease was studied in a 1-year clinical study (ACCENT II). A total of 306 patients received 3 doses of intravenous infliximab 5 mg/kg at week 0, 2 and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. At week 14, 282 patients were assessed for clinical response and randomised to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46.

Week-14 responders (195/282) were analysed for the primary endpoint, which was time from randomisation to loss of response (see Table 9). Corticosteroid tapering was permitted after week 6.

**Table 9**
**Effects on response rate, data from ACCENT II (Week-14 responders)**

| | ACCENT II (Week-14 responders) | | |
|---|---|---|---|
| | Placebo Maintenance (n=99) | Infliximab Maintenance (5 mg/kg) (n=96) | p-value |
| Median time to loss of response through week 54 | 14 weeks | >40 weeks | <0.001 |
| **Week 54** | | | |
| Fistula Response (%)[a] | 23.5 | 46.2 | 0.001 |
| Complete fistula response (%)[b] | 19.4 | 36.3 | 0.009 |

a A ≥50% reduction from baseline in the number of draining fistulas over a period of ≥4 weeks.
b Absence of any draining fistulas.

Beginning at week 22, patients who initially responded to treatment and subsequently lost their response were eligible to cross over to active re-treatment every 8 weeks at a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Among patients in the infliximab 5 mg/kg group who crossed over because of loss of fistula response after week 22, 57% (12/21) responded to re-treatment with infliximab 10 mg/kg every 8 weeks.

There was no significant difference between placebo and infliximab for the proportion of patients with sustained closure of all fistulas through week 54, for symptoms such as proctalgia, abscesses and urinary tract infection or for number of newly developed fistulas during treatment.

Maintenance therapy with infliximab every 8 weeks significantly reduced disease-related hospitalisations and surgeries compared with placebo. Furthermore, a reduction in corticosteroid use and improvements in quality of life were observed.

*Subcutaneous formulation*

The efficacy of subcutaneous infliximab in active Crohn's disease and active ulcerative colitis patients was assessed in an open-label, randomised, parallel-group, Phase I study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of PK of subcutaneous infliximab compared to intravenous infliximab treatment.

In Part 1 of this study, 45 patients with active Crohn's disease were enrolled to receive 2 doses of Remsima 5 mg/kg intravenously at Weeks 0 and 2 and subsequently 44 patients were randomised into four cohorts to receive Remsima 5 mg/kg intravenously (n=13) at Week 6 and every 8 weeks up to Week 54, Remsima 120 mg subcutaneously (n=11), Remsima 180 mg subcutaneously (n=12) or Remsima 240 mg subcutaneously (n=8) at Week 6 and every 2 weeks up to Week 54.

In Part 2 of this study, among 136 patients (57 patients with active Crohn's disease and 79 patients with active ulcerative colitis) who were enrolled to receive 2 doses of Remsima 5 mg/kg intravenously at Weeks 0 and 2, 66 patients (28 patients with active Crohn's disease and 38 patients with active ulcerative colitis) were randomised to receive Remsima 120/ 240 mg subcutaneously at Week 6 and every 2 weeks up to Week 54, while 65 patients (25 patients with active Crohn's disease and 40 patients with active ulcerative colitis) were randomised to receive Remsima 5 mg/kg intravenously at Week 6, 14 and 22 and then switched to Remsima 120/ 240 mg subcutaneous formulation at Week 30 once-every 2 weeks up to Week 54. The dosage of Remsima 120/ 240 mg subcutaneous formulation was determined based on the patient's body weight at Week 6 for those who received Remsima subcutaneously and at Week 30 for those who switched to Remsima subcutaneous formulation (Remsima subcutaneous 120 mg for patients <80 kg; 240 mg for patients ≥80 kg).

In active Crohn's disease patients, the descriptive efficacy results following Remsima 120 mg subcutaneous formulation were generally comparable to Remsima 5 mg/kg intravenous formulation in terms of clinical response (CDAI-70 response defined as a decrease in CDAI by ≥70 points and CDAI-100 response defined as ≥100 points from baseline), clinical remission (defined as an absolute CDAI score of <150 points) and endoscopy assessments (endoscopic response defined as a decrease in ≥50% of overall Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) score from the baseline value and endoscopic remission defined as an absolute SES-CD score of ≤2 points).

The efficacy of subcutaneous infliximab in active Crohn's disease patients was also assessed in a randomized, double-blind, placebo-controlled clinical study in 343 adult patients with moderately to severely active CD (CDAI of 220 to 450 points) with an inadequate response to conventional therapies (LIBERTY-CD). Concomitant treatment with stable doses of aminosalicylates, corticosteroids, antibiotics and/or immunomodulatory agents were permitted. Corticosteroids dose was tapered after Week 10. Patients who were classified as CDAI-100 responders at Week 10 following three IV

infusions of infliximab 5 mg/kg at Weeks 0, 2 and 6 were randomized to receive an injection of either subcutaneous infliximab 120 mg or placebo every 2 weeks thereafter from Week 10 through Week 54.

The co-primary endpoints were clinical remission (based on CDAI) and endoscopic response at Week 54. Clinical remission was defined as an absolute CDAI score of <150 points, and endoscopic response was defined as a 50% decrease in SES-CD score from the baseline value.
Key secondary endpoints were CDAI -100 response and endoscopic remission at Week 54.

In LIBERTY-CD, patients treated with subcutaneous infliximab at the recommended dosage (120 mg every 2 weeks) achieved clinical remission (based on CDAI), endoscopic response, CDAI-100 response, and endoscopic remission more often compared to placebo (Table 10).

**Table 10**
**Clinical Remission, Endoscopic Response, CDAI-100 Response and Endoscopic Remission in LIBERTY-CD**

| Endpoint[a] | Infliximab sc 120 mg (N=231) | Placebo (N=112) | Treatment Difference and 95% CI |
|---|---|---|---|
| **Clinical remission (based on CDAI) at Week 54[b]** | 62.3% | 32.1% | 32.1% (20.9, 42.1) |
| **Endoscopic response at Week 54[c]** | 51.1% | 17.9% | 34.6% (24.1, 43.5) |
| **CDAI-100 response at Week 54[d]** | 65.8% | 38.4% | 28.9% (17.7, 39.2) |
| **Endoscopic remission at Week 54[e]** | 34.6% | 10.7% | 24.9% (15.4, 32.8) |

a Patient who had loss of response between Week 22 and 54 were allowed to switch to 240 mg infliximab sc both in the infliximab and placebo arms. The patients who switched are considered non-responders.
b Defined as an absolute CDAI score of <150 points.
c Defined as a 50% decrease in SES-CD score from the baseline value.
d Defined as a decrease in CDAI score of 100 points or more from the baseline value.
e Defined as an absolute SES-CD score of ≤4 and at least 2-point reduction from the baseline value with no sub-score of >1.

In LIBERTY-CD, dose adjustment to subcutaneous infliximab 240 mg was allowed from Week 22 for patients who initially responded but then lost response in both subcutaneous infliximab 120 mg and placebo groups. Loss of response was defined as an increase in CDAI of ≥100 points from the Week 10 CDAI score with a total score ≥220. Among patients who were responders to intravenous infliximab at week 10, who met loss of response criteria at or after week 22 and received a dose increase to subcutaneous infliximab 240 mg, 21/34 (61.8%) had regained CDAI-100 response at Week 54. Spontaneous regain of response, without dose adjustment, occurred in 1/7 patients in each group (infliximab sc 120 mg and placebo). Including an open-label extension phase of the LIBERTY-CD study, overall 73 patients have received infliximab 240 mg as maintenance treatment for at least 44 weeks with no relevant additional safety findings compared to the 120 mg dose.

In LIBERTY-CD, the impact of use of immunosuppressant (azathioprine, 6-mercaptopurine and methotrexate) on efficacy was evaluated. There was no significant difference between patients with and without immunosuppressants in the primary and the key secondary efficacy endpoints.

*Adult ulcerative colitis*

*Intravenous formulation*

The safety and efficacy of intravenous infliximab were assessed in two (ACT 1 and ACT 2) randomised, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) with an inadequate response to conventional therapies [oral corticosteroids, aminosalicylates and/or immunomodulators (6-MP, AZA)]. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In both studies, patients were randomised to receive either placebo, 5 mg/kg infliximab, or 10 mg/kg infliximab at weeks 0, 2, 6, 14 and 22, and in ACT 1 at weeks 30, 38 and 46. Corticosteroid taper was permitted after week 8.

**Table 11**
**Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2**

| | | Infliximab | | |
|---|---|---|---|---|
| | Placebo | 5 mg/kg | 10 mg/kg | Combined |
| Subjects randomised | 244 | 242 | 242 | 484 |
| **Percentage of subjects in clinical response and in sustained clinical response** | | | | |
| Clinical response at Week 8[a] | 33.2% | 66.9% | 65.3% | 66.1% |
| Clinical response at Week 30[a] | 27.9% | 49.6% | 55.4% | 52.5% |
| Sustained response (clinical response at both Week 8 and Week 30)[a] | 19.3% | 45.0% | 49.6% | 47.3% |
| **Percentage of subjects in clinical remission and sustained remission** | | | | |
| Clinical remission at Week 8[a] | 10.2% | 36.4% | 29.8% | 33.1% |
| Clinical remission at Week 30[a] | 13.1% | 29.8% | 36.4% | 33.1% |
| Sustained remission(in remission at both Week 8 and Week 30)[a] | 5.3% | 19.0% | 24.4% | 21.7% |
| **Percentage of subjects with mucosal healing** | | | | |
| Mucosal healing at Week 8[a] | 32.4% | 61.2% | 60.3% | 60.7% |
| Mucosal healing at Week 30[a] | 27.5% | 48.3% | 52.9% | 50.6% |

a $p < 0.001$, for each infliximab treatment group vs. placebo.

The efficacy of infliximab through week 54 was assessed in the ACT 1 study.
At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p<0.001$). Clinical remission and mucosal healing occurred in a greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.6% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportions of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in the placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

A greater proportion of patients in the combined infliximab treatment group were able to discontinue corticosteroids while remaining in clinical remission compared to the placebo treatment group at both week 30 (22.3% vs. 7.2%, $p <0.001$, pooled ACT 1 & ACT 2 data) and week 54 (21.0% vs. 8.9%, $p=0.022$, ACT 1 data).

The pooled data analysis from the ACT 1 and ACT 2 studies and their extensions, analysed from baseline through 54 weeks, demonstrated a reduction of ulcerative colitis-related hospitalisations and surgical procedures with infliximab treatment. The number of ulcerative colitis-related hospitalisations was significantly lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of hospitalisations per 100 subject-years: 21 and 19 vs. 40 in the placebo group; $p=0.019$ and $p=0.007$, respectively). The number of ulcerative colitis-related surgical procedures was also lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of surgical procedures per 100 subject-years: 22 and 19 vs. 34; $p=0.145$ and $p=0.022$, respectively).

The proportion of subjects who underwent colectomy at any time within 54 weeks following the first infusion of study agent were collected and pooled from the ACT 1 and ACT 2 studies and their

extensions. Fewer subjects underwent colectomy in the 5 mg/kg infliximab group (28/242 or 11.6% [N.S.]) and the 10 mg/kg infliximab group (18/242 or 7.4% [p=0.011]) than in the placebo group (36/244; 14.8%).

The reduction in incidence of colectomy was also examined in another randomised, double-blind study (C0168Y06) in hospitalised patients (n=45) with moderately to severely active ulcerative colitis who failed to respond to intravenous corticosteroids and who were therefore at higher risk for colectomy. Significantly fewer colectomies occurred within 3 months of study infusion in patients who received a single dose of 5 mg/kg infliximab compared to patients who received placebo (29.2% vs. 66.7% respectively, p=0.017).

In ACT 1 and ACT 2, infliximab improved quality of life, confirmed by statistically significant improvement in both a disease specific measure, IBDQ, and by improvement in the generic 36-item short form survey SF-36.

*Subcutaneous formulation*

The efficacy of subcutaneous infliximab in active ulcerative colitis patients was assessed in Part 2 of an open-label, randomised, parallel-group, Phase I study. For study details, see Section 5.1 on Crohn's disease, subcutaneous formulation.

In active ulcerative colitis patients, the descriptive efficacy results following Remsima 120 mg subcutaneous formulation were generally comparable to Remsima 5 mg/kg intravenous formulation in terms of clinical response (defined as a decrease from baseline in total Mayo score of at least 3 points and at least 30% or a decrease from baseline in partial Mayo score at least 2 points, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1), clinical remission (defined as a total Mayo score of ≤2 points with no individual subscore exceeding 1 point, or partial Mayo score of ≤1 point) and mucosal healing (defined as absolute endoscopic subscore of 0 or 1 from Mayo Scoring System).

*Adult ankylosing spondylitis*

*Intravenous formulation*

Efficacy and safety of infliximab intravenous formulation were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain ≥ 4 on a scale of 1-10).

In the first study (P01522), which had a 3-month double-blind phase, 70 patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). At week 12, placebo patients were switched to infliximab 5 mg/kg every 6 weeks up to week 54. After the first year of the study, 53 patients continued into an open-label extension to week 102.

In the second clinical study (ASSERT), 279 patients were randomised to receive either placebo (Group 1, n=78) or 5 mg/kg infliximab (Group 2, n=201) at 0, 2 and 6 weeks and every 6 weeks to week 24. Thereafter, all subjects continued on infliximab every 6 weeks to week 96. Group 1 received 5 mg/kg infliximab. In Group 2, starting with the week 36 infusion, patients who had a BASDAI ≥3 at 2 consecutive visits, received 7.5 mg/kg infliximab every 6 weeks thereafter through week 96.

In ASSERT, improvement in signs and symptoms was observed as early as week 2. At week 24, the number of ASAS 20 responders was 15/78 (19%) in the placebo group, and 123/201 (61%) in the 5 mg/kg infliximab group (p<0.001). There were 95 subjects from group 2 who continued on 5 mg/kg every 6 weeks. At 102 weeks there were 80 subjects still on infliximab treatment and among those, 71 (89%) were ASAS 20 responders.

In P01522, improvement in signs and symptoms was also observed as early as week 2. At week 12, the number of BASDAI 50 responders were 3/35 (9%) in the placebo group, and 20/35 (57%) in the 5 mg/kg group ($p<0.01$). There were 53 subjects who continued on 5 mg/kg every 6 weeks. At 102 weeks there were 49 subjects still on infliximab treatment and among those, 30 (61%) were BASDAI 50 responders.

In both studies, physical function and quality of life as measured by the BASFI and the physical component score of the SF-36 were also improved significantly.

*Adult psoriatic arthritis*

*Intravenous formulation*

Efficacy and safety of infliximab intravenous formulation were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active psoriatic arthritis.

In the first clinical study (IMPACT), efficacy and safety of infliximab were studied in 104 patients with active polyarticular psoriatic arthritis. During the 16-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, and 14 (52 patients in each group). Starting at week 16, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 8 weeks up to week 46. After the first year of the study, 78 patients continued into an open-label extension to week 98.

In the second clinical study (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints). Forty six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, 47 placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46.

Key efficacy results for IMPACT and IMPACT 2 are shown in Table 12 below:

**Table 12**
**Effects on ACR and PASI in IMPACT and IMPACT 2**

| | IMPACT | | | IMPACT 2* | | |
|---|---|---|---|---|---|---|
| | Placebo (Week 16) | Infliximab (Week 16) | Infliximab (Week 98) | Placebo (Week 24) | Infliximab (Week 24) | Infliximab (Week 54) |
| Patients randomised | 52 | 52 | N/A[a] | 100 | 100 | 100 |
| ACR response (% of patients) N | 52 | 52 | 78 | 100 | 100 | 100 |
| ACR 20 response* | 5 (10%) | 34 (65%) | 48 (62%) | 16 (16%) | 54 (54%) | 53 (53%) |
| ACR 50 response* | 0 (0%) | 24 (46%) | 35 (45%) | 4 (4%) | 41 (41%) | 33 (33%) |
| ACR 70 response* | 0 (0%) | 15 (29%) | 27 (35%) | 2 (2%) | 27 (27%) | 20 (20%) |
| PASI response (% of patients)[b] N | | | | 87 | 83 | 82 |

| | | | |
|---|---|---|---|
| PASI 75 response** | 1 (1%) | 50 (60%) | 40 (48.8%) |

* ITT-analysis where subjects with missing data were included as non-responders.
a Week 98 data for IMPACT includes combined placebo crossover and infliximab patients who entered the open-label extension.
b Based on patients with PASI >2.5 at baseline for IMPACT, and patients with >3% BSA psoriasis skin involvement at baseline in IMPACT 2.
** PASI 75 response for IMPACT not included due to low N; $p<0.001$ for infliximab vs. placebo at week 24 for IMPACT 2.

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54, respectively. Efficacy has been demonstrated with or without concomitant use of methotrexate. Decreases in parameters of peripheral activity characteristic of psoriatic arthritis (such as number of swollen joints, number of painful/tender joints, dactylitis and presence of enthesopathy) were seen in the infliximab-treated patients.

Radiographic changes were assessed in IMPACT 2. Radiographs of hands and feet were collected at baseline, weeks 24 and 54. Infliximab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at the week 24 primary endpoint as measured by change from baseline in total modified vdH-S score (mean ± SD score was 0.82 ± 2.62 in the placebo group compared with -0.70 ± 2.53 in the infliximab group; $p<0.001$). In the infliximab group, the mean change in total modified vdH-S score remained below 0 at the week 54 timepoint.

Infliximab-treated patients demonstrated significant improvement in physical function as assessed by HAQ. Significant improvements in health-related quality of life were also demonstrated as measured by the physical and mental component summary scores of the SF-36 in IMPACT 2.

*Adult psoriasis*

*Intravenous formulation*

The efficacy of infliximab intravenous formulation was assessed in two multicentre, randomised, double-blind studies: SPIRIT and EXPRESS. Patients in both studies had plaque psoriasis (Body Surface Area [BSA] ≥10% and Psoriasis Area and Severity Index [PASI] score ≥12). The primary endpoint in both studies was the percent of patients who achieved ≥75% improvement in PASI from baseline at week 10.

SPIRIT evaluated the efficacy of infliximab induction therapy in 249 patients with plaque psoriasis that had previously received PUVA or systemic therapy. Patients received either 3 or 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6. Patients with a PGA score ≥3 were eligible to receive an additional infusion of the same treatment at week 26.
In SPIRIT, the proportion of patients achieving PASI 75 at week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p<0.001$). By week 26, twenty weeks after the last induction dose, 30% of patients in the 5 mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of >20 weeks. No rebound was observed.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis. Patients received 5 mg/kg infliximab- or placebo-infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8 weeks through week 22 in the placebo group and through week 46 in the infliximab group. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg). Nail psoriasis was assessed using the Nail Psoriasis Severity Index (NAPSI). Prior therapy with PUVA, methotrexate, ciclosporin, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in Table 13. In infliximab treated subjects, significant PASI 50 responses were apparent at the first visit (week 2) and PASI 75 responses by the second visit (week 6).

Efficacy was similar in the subgroup of patients that were exposed to previous systemic therapies compared to the overall study population.

**Table 13**
**Summary of PASI response, PGA response and percent of patients with all nails cleared at Weeks 10, 24 and 50. EXPRESS**

| | Placebo → Infliximab 5 mg/kg (at week 24) | Infliximab 5 mg/kg |
|---|---|---|
| **Week 10** | | |
| N | 77 | 301 |
| ≥90% improvement | 1 (1.3%) | 172 (57.1%) [a] |
| ≥75% improvement | 2 (2.6%) | 242 (80.4%) [a] |
| ≥50% improvement | 6 (7.8%) | 274 (91.0%) |
| PGA of cleared (0) or minimal (1) | 3 (3.9%) | 242 (82.9%) [ab] |
| PGA of cleared (0), minimal (1), or mild (2) | 14 (18.2%) | 275 (94.2%) [ab] |
| **Week 24** | | |
| N | 77 | 276 |
| ≥90% improvement | 1 (1.3%) | 161 (58.3%) [a] |
| ≥75% improvement | 3 (3.9%) | 227 (82.2%) [a] |
| ≥50% improvement | 5 (6.5%) | 248 (89.9%) |
| PGA of cleared (0) or minimal (1) | 2 (2.6%) | 203 (73.6%) [a] |
| PGA of cleared (0), minimal (1), or mild (2) | 15 (19.5%) | 246 (89.1%) [a] |
| **Week 50** | | |
| N | 68 | 281 |
| ≥90% improvement | 34 (50.0%) | 127 (45.2%) |
| ≥75% improvement | 52 (76.5%) | 170 (60.5%) |
| ≥50% improvement | 61 (89.7%) | 193 (68.7%) |
| PGA of cleared (0) or minimal (1) | 46 (67.6%) | 149 (53.0%) |
| PGA of cleared (0), minimal (1), or mild (2) | 59 (86.8%) | 189 (67.3%) |
| **All nails cleared[c]** | | |
| Week 10 | 1/65(1.5%) | 16/235 (6.8%) |
| Week 24 | 3/65 (4.6%) | 58/223 (26.0%) [a] |
| Week 50 | 27/64 (42.2%) | 92/226 (40.7%) |

a $p < 0.001$, for each infliximab treatment group vs. control.
b n = 292.
c Analysis was based on subjects with nail psoriasis at baseline (81.8% of subjects). Mean baseline NAPSI scores were 4.6 and 4.3 in infliximab and placebo group.

Significant improvements from baseline were demonstrated in DLQI ($p<0.001$) and the physical and mental component scores of the SF 36 ($p<0.001$ for each component comparison).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing infliximab in all subsets of the paediatric population in rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and Crohn's disease (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Absorption and distribution

Single subcutaneous injections of 120, 180 and 240 mg of infliximab yielded approximately dose proportional increases in the maximum serum concentration ($C_{max}$) and area under the concentration-time curve (AUC). The apparent volume of distribution during the terminal phase (mean of 7.3 to 8.8 litres) was not dependent on the administered dose.

After single doses of 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects, the mean $C_{max}$ values were 10.0, 15.1 and 23.1 µg/mL, respectively, and for all doses infliximab could be detected in the serum for at least 12 weeks thereafter.

The bioavailability of subcutaneous infliximab, estimated in a population PK model, was 62% (95% CI: 60% - 64%).

After administration of infliximab 120 mg subcutaneously every 2 weeks (from Week 6 after 2 doses of intravenous infliximab at Weeks 0 and 2) to patients with active rheumatoid arthritis who were concomitantly treated with MTX, the median (CV%) $C_{trough}$ level at Week 22 (steady state) was 12.8 µg/mL (80.1%).

After administration of infliximab 120 mg subcutaneously every 2 weeks (from Week 6 after 2 doses of intravenous infliximab at Weeks 0 and 2) to patients with active Crohn's disease and active ulcerative colitis, the median (CV%) $C_{trough}$ level at Week 22 (steady state) was 20.1 µg/mL (48.9%).

Based on PK results from clinical studies in patients with active rheumatoid arthritis, active Crohn's disease and active ulcerative colitis and population PK modelling, $C_{trough}$ levels at steady state would be higher after administration of infliximab 120 mg subcutaneous formulation given every 2 weeks compared with infliximab 5 mg/kg intravenous formulation given every 8 weeks.

For the dosing regimen with subcutaneous loading in patients with rheumatoid arthritis, the predicted median AUC value was 17,400 µg·h/mL from Week 0 to 6 which was approximately 1.8 fold lower than the predicted median AUC value for the dosing regimen with infliximab intravenous loading doses (32,100 µg·h/mL). Whereas, the predicted median AUC values from Week 6 to 14 were comparable between the two dosing regimens with subcutaneous loading and intravenous loading (19,600 and 18,100 µg·h/mL, respectively).

Elimination

The elimination pathways for infliximab have not been characterised. Unchanged infliximab was not detected in urine. No major age- or weight-related differences in clearance or volume of distribution were observed in rheumatoid arthritis patients.

In studies in healthy subjects, the mean (± SD) apparent clearance of Remsima 120 mg administered subcutaneously was 19.3 ± 6.9 mL/hr.

In the RA patients, the mean (± SD) apparent clearance of Remsima 120 mg subcutaneous at steady state was 18.8 ± 8.3 mL/hr. In the active Crohn's disease and active ulcerative colitis patients, the mean (± SD) apparent clearance of Remsima 120 mg subcutaneous at steady state was 16.1 ± 6.9 mL/hr.

The mean terminal half-life ranged from 11.3 days to 13.7 days for 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects.

Special populations

*Elderly*

The pharmacokinetics of infliximab injected via subcutaneous route in elderly patients has not been studied.

*Paediatric population*

Subcutaneous administration of Remsima is not recommended for paediatric use and no data are available on the use of Remsima administered subcutaneously in the paediatric population.

*Hepatic and renal impairment*

Studies with infliximab have not been performed in patients with liver or renal disease.

### 5.3 Preclinical safety data

Infliximab does not cross react with TNFα from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse TNFα, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.

Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNFα demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

The subcutaneous administration of Remsima to New Zealand White rabbits was well tolerated at the actual concentration to be used in humans.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Acetic acid
Sodium acetate trihydrate
Sorbitol (E420)
Polysorbate 80 (E433)
Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

4 years

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the pre-filled syringe/pre-filled pen in the outer carton in order to protect from light.

The medicinal product may be stored at temperatures up to a maximum of 25°C for a period of up to 28 days. The medicinal product must be discarded if not used within the 28-day period.

### 6.5 Nature and contents of container

Remsima 120 mg solution for injection in pre-filled syringe
Remsima 120 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:
- 1 prefilled syringe (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled syringes (1 mL sterile solution) with 2 alcohol pads.
- 4 prefilled syringes (1 mL sterile solution) with 4 alcohol pads.
- 6 prefilled syringes (1 mL sterile solution) with 6 alcohol pads.

Remsima 120 mg solution for injection in pre-filled syringe with automatic needle guard
Remsima 120 mg solution for injection in single-use pre-filled syringe with automatic needle guard. The syringe is made from type I glass with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:
- 1 prefilled syringe with automatic needle guard (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled syringes with automatic needle guard (1 mL sterile solution) with 2 alcohol pads.
- 4 prefilled syringes with automatic needle guard (1 mL sterile solution) with 4 alcohol pads.
- 6 prefilled syringes with automatic needle guard (1 mL sterile solution) with 6 alcohol pads.

Remsima 120 mg solution for injection in pre-filled pen
Remsima 120 mg solution for injection in single-use pre-filled pen. The syringe inside the pen is made from type 1 glass with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:
- 1 prefilled pen (1 mL sterile solution) with 2 alcohol pads.
- 2 prefilled pens (1 mL sterile solution) with 2 alcohol pads.
- 4 prefilled pens (1 mL sterile solution) with 4 alcohol pads.
- 6 prefilled pens (1 mL sterile solution) with 6 alcohol pads.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Remsima is a solution that is clear to opalescent, colourless to pale brown. Do not use if the solution is cloudy, discoloured or contains visible particulate matter.

After use, place the pre-filled syringe/ pre-filled syringe with automatic needle guard/ pre-filled pen into a puncture resistant container and discard as required by local regulations. Do not recycle the injecting device. Always keep the medicinal product out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest

Váci út 1-3. WestEnd Office Building B torony
Hungary

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/006
EU/1/13/853/007
EU/1/13/853/008
EU/1/13/853/009
EU/1/13/853/010
EU/1/13/853/011
EU/1/13/853/012
EU/1/13/853/013
EU/1/13/853/014
EU/1/13/853/015
EU/1/13/853/016
EU/1/13/853/017

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2019

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 40 mg/mL concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Remsima 100 mg concentrate for solution for infusion
Each mL contains 40 mg of infliximab*.
Each vial contains 100 mg of infliximab*.

Remsima 350 mg concentrate for solution for infusion
Each mL contains 40 mg of infliximab*.
Each vial contains 350 mg of infliximab*.

* Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

Excipient(s) with known effect

This medicine contains 45 mg sorbitol (E420) and 0.5 mg polysorbate 80 (E433) in each mL of concentrate for solution for infusion.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear to opalescent solution, colourless to pale brown liquid with pH of 5.0 ± 0.2 and osmolality of 276 - 346 mOsmol/kg.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Rheumatoid arthritis

Remsima, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated (see section 5.1).

Adult Crohn's disease

Remsima is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's disease

Remsima is indicated for treatment of severe, active Crohn's disease in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative colitis

Remsima is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric ulcerative colitis

Remsima is indicated for treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

Ankylosing spondylitis

Remsima is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Remsima is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
Remsima should be administered:

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1).

Psoriasis

Remsima is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).

## 4.2 Posology and method of administration

Remsima treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, ankylosing spondylitis, psoriatic arthritis or psoriasis. Remsima should be administered intravenously. Remsima infusions should be administered by qualified healthcare professionals trained to detect any infusion-related issues. Patients treated with Remsima should be given the package leaflet and the patient reminder card.

During Remsima treatment, other concomitant therapies, e.g. corticosteroids and immunosuppressants should be optimised.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed. Remsima subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Posology

*Adults (≥18 years)*

*Rheumatoid arthritis*
3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Remsima must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, consideration may be given to increase the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

*Moderately to severely active Crohn's disease*
5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

In responding patients, the alternative strategies for continued treatment are:
- Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur (see 'Re-administration' below and section 4.4).

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

*Fistulising, active Crohn's disease*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given.

In responding patients, the alternative strategies for continued treatment are:
- Maintenance: Additional infusions of 5 mg/kg every 8 weeks or
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks (see 'Re-administration' below and section 4.4).

Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

*Ulcerative colitis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

*Ankylosing spondylitis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

*Psoriatic arthritis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

*Psoriasis*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

*Re-administration for Crohn's disease and rheumatoid arthritis*
If the signs and symptoms of disease recur, infliximab can be re-administered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year (see sections 4.4 and 4.8). The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

*Re-administration for ulcerative colitis*
The safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for ankylosing spondylitis*
The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for psoriatic arthritis*
The safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

*Re-administration for psoriasis*
Limited experience from re-treatment with one single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen (see section 5.1).

Limited experience from re-treatment following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment (see section 4.8).

*Re-administration across indications*
In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen is not recommended (see section 4.8). In this situation, infliximab should be re-initiated as a single dose followed by the maintenance dose recommendations described above.

Special populations

*Elderly*

Specific studies of infliximab in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies. No dose adjustment is required (see section 5.2). For more information about the safety of infliximab in elderly patients (see sections 4.4 and 4.8).

*Renal and/or hepatic impairment*

Infliximab has not been studied in these patient populations. No dose recommendations can be made (see section 5.2).

*Paediatric population*

*Crohn's disease (6 to 17 years)*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment (see section 5.1).

Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should be carefully considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval.

The safety and efficacy of infliximab have not been studied in children with Crohn's disease below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.

*Ulcerative colitis (6 to 17 years)*
5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment (see section 5.1).

The safety and efficacy of infliximab have not been studied in children with ulcerative colitis below the age of 6 years. Currently available pharmacokinetic data are described in section 5.2 but no recommendation on a posology can be made in children younger than 6 years.

*Psoriasis*
The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of psoriasis have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

*Juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis*
The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indications of juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis have not been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

*Juvenile rheumatoid arthritis*
The safety and efficacy of infliximab in children and adolescents younger than 18 years for the indication of juvenile rheumatoid arthritis have not been established. Currently available data are described in sections 4.8 and 5.2 but no recommendation on a posology can be made.

Method of administration

Infliximab should be administered intravenously over a 2-hour period. All patients administered infliximab are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously (see section 4.4).

*Shortened infusions across adult indications*

In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of infliximab (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses >6 mg/kg have not been studied (see section 4.8).

For preparation and administration instructions, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance, to other murine proteins, or to any of the excipients listed in section 6.1.

Patients with hereditary fructose intolerance (HFI). Prior to initiating treatment, HFI should be excluded on age-appropriate clinical grounds (see section 4.4).

Patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see section 4.4).

Patients with moderate or severe heart failure (NYHA class III/IV) (see sections 4.4 and 4.8).

## 4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion reactions and hypersensitivity

Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions (see section 4.8).

Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically-treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further infliximab infusions must not be administered (see section 4.8).

In clinical studies, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval. Patients should be advised to seek immediate medical advice if they experience any delayed adverse reaction (see section 4.8). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with infliximab. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with infliximab must not be given if a patient develops a serious infection or sepsis.

Caution should be exercised when considering the use of infliximab in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Tumour necrosis factor alpha ($TNF_{\alpha}$) mediates inflammation and modulates cellular immune responses. Experimental data show that $TNF_{\alpha}$ is essential for the clearing of intracellular infections. Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab.

It should be noted that suppression of $TNF_{\alpha}$ may mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections and of typical clinical presentation of rare and unusual infections is critical in order to minimise delays in diagnosis and treatment.

Patients taking TNF-blockers are more susceptible to serious infections.

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis.

Patients who develop a new infection while undergoing treatment with infliximab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

*Tuberculosis*

There have been reports of active tuberculosis in patients receiving infliximab. It should be noted that in the majority of these reports tuberculosis was extrapulmonary, presenting as either local or disseminated disease.

Before starting treatment with infliximab, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history

of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, (e.g. tuberculin skin test, chest X-ray, and/or Interferon Gamma Release Assay), should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient reminder card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, infliximab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of infliximab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with antituberculosis therapy before the initiation of infliximab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, antituberculosis therapy should be considered before the initiation of infliximab.

Use of antituberculosis therapy should also be considered before the initiation of infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Some cases of active tuberculosis have been reported in patients treated with infliximab during and after treatment for latent tuberculosis.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after infliximab treatment.

*Invasive fungal infections*

In patients treated with infliximab, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness, and a physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients.

Invasive fungal infections may present as disseminated rather than localised disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of infliximab treatment should be carefully considered before initiation of infliximab therapy.

*Fistulising Crohn's disease*
Patients with fistulising Crohn's disease with acute suppurative fistulas must not initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded (see section 4.3).

Hepatitis B (HBV) reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome.

Patients should be tested for HBV infection before initiating treatment with infliximab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with infliximab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with antiviral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, infliximab should be stopped and effective antiviral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥5 times the upper limit of normal develop(s), infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent administration of TNF-alpha inhibitor and anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another $TNF_{\alpha}$-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other $TNF_{\alpha}$-blocking agents. Therefore, the combination of infliximab and anakinra is not recommended.

Concurrent administration of TNF-alpha inhibitor and abatacept

In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of infliximab and abatacept is not recommended.

Concurrent administration with other biological therapeutics

There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs

Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse reactions, including infection.

Vaccinations

It is recommended that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

In a subset of 90 adult patients with rheumatoid arthritis from the ASPIRE study a similar proportion of patients in each treatment group (methotrexate plus: placebo [n = 17], 3 mg/kg [n = 27] or 6 mg/kg infliximab [n = 46]) mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine, indicating that infliximab did not interfere with T-cell independent humoral immune responses. However, studies from the published literature in various indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) suggest that non-live vaccinations received during treatment with

anti-TNF therapies, including infliximab may elicit a lower immune response than in patients not receiving anti-TNF therapy.

Live vaccines/therapeutic infectious agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with infliximab is not recommended.

Infant exposure *in utero*
In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see section 4.6).

Infant exposure via breast milk
Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see section 4.6).

Therapeutic infectious agents

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with infliximab.

Autoimmune processes

The relative deficiency of $TNF_{\alpha}$ caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab and is positive for antibodies against double-stranded DNA, further treatment with infliximab must not be given (see section 4.8).

Neurological events

Use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical studies of infliximab across all approved indications the incidence of lymphoma in infliximab-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

In an exploratory clinical study evaluating the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Caution should be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking.

With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded (see section 4.8). Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.8).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. Periodic screening should continue in women treated with infliximab, including those over 60 years of age.

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that infliximab treatment influences the risk for developing dysplasia or colon cancer.

Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits of continued therapy to the individual patients should be carefully considered by the clinician.

Heart failure

Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure (see sections 4.3 and 4.8).

Haematologic reactions

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of infliximab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Others

There is limited safety experience of infliximab treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life of infliximab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on infliximab should be closely monitored for infections, and appropriate actions should be taken.

Failure to respond to treatment for Crohn's disease may indicate the presence of a fixed fibrotic stricture that may require surgical treatment. There is no evidence to suggest that infliximab worsens or causes fibrotic strictures.

Special populations

*Elderly*

The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly (see section 4.8).

*Paediatric population*

*Infections*
In clinical studies, infections have been reported in a higher proportion of paediatric patients compared to adult patients (see section 4.8).

*Vaccinations*
It is recommended that paediatric patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating infliximab therapy. Paediatric patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

*Malignancies and lymphoproliferative disorders*
Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with AZA or 6-MP concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.8).

Excipients with known effect

*Sorbitol*

Each mL of this medicinal product contains 45 mg of sorbitol (E420). Patients with hereditary fructose intolerance (HFI) must not take Remsima concentrate for solution for infusion. In HFI patients, a spontaneous aversion for fructose-containing foods develops and may be combined with the onset of symptoms (vomiting, gastro-intestinal disorders, apathy, height and weight retardation). Therefore, a detailed history with regards to HFI symptoms has to be taken of each patient prior to receiving Remsima concentrate for solution for infusion. In case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care (see section 4.3).

*Polysorbate 80*

This medicine contains 1.3 mg of polysorbate 80 in each 100 mg vial which is equivalent to 0.5 mg/mL, and 4.4 mg of polysorbate 80 in each 350 mg vial which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Sodium

Remsima contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free' . Remsima is however, diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.

Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent.

The combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended (see section 4.4).

It is recommended that live vaccines not be given concurrently with infliximab. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for 12 months following birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see section 4.4).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see sections 4.4 and 4.6).

It is recommended that therapeutic infectious agents not be given concurrently with infliximab (see section 4.4).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Pregnancy

The moderate number of prospectively collected pregnancies exposed to infliximab resulting in live birth with known outcomes, including approximately 1,100 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

Based on an observational study from Northern Europe, an increased risk (OR, 95% CI; p-value) for C-section (1.50, 1.14-1.96; p = 0.0032), preterm birth (1.48, 1.05-2.09; p = 0.024), small for gestational age (2.79, 1.54-5.04; p = 0.0007), and low birth weight (2.03, 1.41-2.94; p = 0.0002) was observed in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids, 270 pregnancies) as compared to women exposed to immunomodulators and/or corticosteroids only (6,460 pregnancies). The potential contribution of exposure to infliximab and/or the severity of the underlying disease in these outcomes remains unclear.

Due to its inhibition of $TNF_{\alpha}$, infliximab administered during pregnancy could affect normal immune responses in the newborn. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse $TNF_{\alpha}$, there was no indication of maternal toxicity, embryotoxicity or teratogenicity (see section 5.3).

The available clinical experience is limited. Infliximab should only be used during pregnancy if clearly needed.

Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth (see sections 4.4 and 4.5). If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. Cases of agranulocytosis have also been reported (see section 4.8).

Breast-feeding

Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding.

Fertility

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Remsima may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of infliximab (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for infliximab include HBV reactivation, CHF (congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, paediatric malignancy, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease), and serious infusion reactions (see section 4.4).

Tabulated list of adverse reactions

Table 1 lists the ADRs based on experience from clinical studies as well as adverse reactions, some with fatal outcome, reported from post-marketing experience. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 1**
**Adverse reactions in clinical studies and from post-marketing experience**

| | |
|---|---|
| *Infections and infestations* | |
| Very common: | Viral infection (e.g. influenza, herpes virus infection, COVID-19*). |
| Common: | Bacterial infections (e.g. sepsis, cellulitis, abscess). |
| Uncommon: | Tuberculosis, fungal infections (e.g. candidiasis, onychomycosis). |
| Rare: | Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation. |
| Not known: | Vaccine breakthrough infection (after *in utero* exposure to infliximab)*. |
| *Neoplasms benign, malignant and unspecified (including cysts and polyps)* | |
| Rare: | Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer. |
| Not known: | Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease and ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma. |
| *Blood and lymphatic system disorders* | |
| Common: | Neutropenia, leukopenia, anaemia, lymphadenopathy. |
| Uncommon: | Thrombocytopenia, lymphopenia, lymphocytosis. |
| Rare: | Agranulocytosis (including infants exposed *in utero* to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura. |
| *Immune system disorders* | |

| | |
|---|---|
| Common: | Allergic respiratory symptom. |
| Uncommon: | Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction. |
| Rare | Anaphylactic shock, vasculitis, sarcoid-like reaction |
| *Metabolism and nutrition disorders* | |
| Uncommon: | Dyslipidaemia. |
| *Psychiatric disorders* | |
| Common: | Depression, insomnia. |
| Uncommon: | Amnesia, agitation, confusion, somnolence, nervousness. |
| Rare: | Apathy. |
| *Nervous system disorders* | |
| Very common: | Headache. |
| Common: | Vertigo, dizziness, hypoaesthesia, paraesthesia. |
| Uncommon: | Seizure, neuropathy. |
| Rare: | Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy). |
| Not known: | Cerebrovascular accidents in close temporal association with infusion. |
| *Eye disorders* | |
| Common | Conjunctivitis |
| Uncommon | Keratitis, periorbital oedema, hordeolum |
| Rare | Endophthalmitis |
| Not known | Transient visual loss occurring during or within 2 hours of infusion |
| *Cardiac disorders* | |
| Common | Tachycardia, palpitation |
| Uncommon | Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia |
| Rare | Cyanosis, pericardial effusion |
| Not known | Myocardial ischaemia/myocardial infarction |
| *Vascular disorders* | |
| Common | Hypotension, hypertension, ecchymosis, hot flush, flushing |
| Uncommon | Peripheral ischaemia, thrombophlebitis, haematoma |
| Rare | Circulatory failure, petechia, vasospasm |
| *Respiratory, thoracic and mediastinal disorders* | |
| Very common | Upper respiratory tract infection, sinusitis |
| Common | Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis |
| Uncommon | Pulmonary oedema, bronchospasm, pleurisy, pleural effusion |
| Rare | Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis) |

| | |
|---|---|
| *Gastrointestinal disorders* | |
| Very common: | Abdominal pain, nausea |
| Common: | Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation |
| Uncommon | Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis |
| *Hepatobiliary disorders* | |
| Common: | Hepatic function abnormal, transaminases increased. |
| Uncommon: | Hepatitis, hepatocellular damage, cholecystitis. |
| Rare: | Autoimmune hepatitis, jaundice. |
| Not known: | Liver failure. |
| *Skin and subcutaneous tissue disorders* | |
| Common: | New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia. |
| Uncommon: | Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation. |
| Rare: | Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions. |
| Not known: | Worsening of symptoms of dermatomyositis. |
| *Musculoskeletal and connective tissue disorders* | |
| Common: | Arthralgia, myalgia, back pain. |
| *Renal and urinary disorders* | |
| Common: | Urinary tract infection. |
| Uncommon: | Pyelonephritis. |
| *Reproductive system and breast disorders* | |
| Uncommon: | Vaginitis. |
| *General disorders and administration site conditions* | |
| Very common: | Infusion-related reaction, pain. |
| Common: | Chest pain, fatigue, fever, injection site reaction, chills, oedema. |
| Uncommon: | Impaired healing. |
| Rare: | Granulomatous lesion. |
| *Investigations* | |
| Uncommon: | Autoantibody positive, weight increased[1]. |
| Rare: | Complement factor abnormal. |

* COVID-19 was seen with the SC administered Remsima

** including bovine tuberculosis (disseminated BCG infection), see section 4.4

[1] At month 12 of the controlled period for adult clinical trials across all indications, the median weight increase was 3.50 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects. The median weight increase for inflammatory bowel disease indications was 4.14 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects, and the median weight increase for rheumatology indications was 3.40 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects.

Description of selected adverse drug reactions

Infusion-related reactions

An infusion-related reaction was defined in clinical studies as any adverse event occurring during an infusion or within 1 hour after an infusion. In phase III clinical studies, 18% of infliximab-treated patients compared with 5% of placebo-treated patients experienced an infusion-related reaction. Overall, a higher proportion of patients receiving infliximab monotherapy experienced an infusion-related reaction compared to patients receiving infliximab with concomitant immunomodulators. Approximately 3% of patients discontinued treatment due to infusion-related reactions and all patients recovered with or without medical therapy. Of infliximab-treated patients who had an infusion reaction during the induction period, through week 6, 27% experienced an infusion reaction during the maintenance period, week 7 through week 54. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), infusions were to be administered over 2 hours for the first 3 infusions. The duration of subsequent infusions could be shortened to not less than 40 minutes in patients who did not experience serious infusion reactions. In this trial, sixty six percent of the patients (686 out of 1,040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1,040) received at least one shortened infusion of 60 minutes or less. Of the infliximab-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15% of patients and serious infusion reactions occurred in 0.4% of patients.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving infliximab monotherapy, 5% (9/179) of patients receiving infliximab in combination with AZA, and 5.6% (9/161) of patients receiving AZA monotherapy. One serious infusion reaction (<1%) occurred in a patient on infliximab monotherapy.

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with infliximab administration (see section 4.4). Cases of transient visual loss occurring during or within 2 hours of infliximab infusion have been reported. Events (some fatal) of myocardial ischaemia/infarction and arrhythmia have been reported, some in close temporal association with infusion of infliximab; cerebrovascular accidents have also been reported in close temporal association with infusion of infliximab.

Infusion reactions following re-administration of infliximab

A clinical study in patients with moderate to severe psoriasis was designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab (maximum of four infusions at 0, 2, 6 and 14 weeks) following disease flare. Patients did not receive any concomitant immunosuppressant therapy. In the re-treatment arm, 4% (8/219) of patients experienced a serious infusion reaction versus <1% (1/222) on maintenance therapy. The majority of serious infusion reactions occurred during the second infusion at week 2. The interval between the last maintenance dose and the first re-induction dose ranged from 35-231 days. Symptoms included, but were not limited to, dyspnoea, urticaria, facial oedema, and hypotension. In all cases, infliximab treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed hypersensitivity

In clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year. In the psoriasis studies, delayed hypersensitivity reactions occurred early in the treatment course. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients experiencing pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and headache.

There are insufficient data on the incidence of delayed hypersensitivity reactions after infliximab-free intervals of more than 1 year but limited data from clinical studies suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval (see section 4.4).

In a 1-year clinical study with repeated infusions in patients with Crohn's disease (ACCENT I study), the incidence of serum sickness-like reactions was 2.4%.

Immunogenicity

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion-related reactions.
In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 14% of patients with any immunosuppressant therapy, and in 24% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 8% of patients developed antibodies to infliximab. In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15% of patients (antibodies occurred in 4% of patients receiving methotrexate and in 26% of patients not receiving methotrexate at baseline). In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy. In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab (see section 4.4: "Infusion reactions and hypersensitivity").

Infections

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis (see section 4.4).

In clinical studies 36% of infliximab-treated patients were treated for infections compared with 25% of placebo-treated patients.

In rheumatoid arthritis clinical studies, the incidence of serious infections including pneumonia was higher in infliximab plus methotrexate-treated patients compared with methotrexate alone especially at doses of 6 mg/kg or greater (see section 4.4).

In post-marketing spontaneous reporting, infections are the most common serious adverse reaction. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported (see section 4.4).

Malignancies and lymphoproliferative disorders

In clinical studies with infliximab in which 5,780 patients were treated, representing 5,494 patient years, 5 cases of lymphomas and 26 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1,600 placebo-treated patients representing 941 patient years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6,234 patients-years (3,210 patients), 5 cases of lymphoma and 38 cases of non-lymphoma malignancies were reported.

Cases of malignancies, including lymphoma, have also been reported in the post-marketing setting (see section 4.4).

In an exploratory clinical study involving patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 adult patients were treated with infliximab at doses similar to those used in rheumatoid arthritis and Crohn's disease. Nine of these patients developed malignancies, including 1 lymphoma. The median duration of follow-up was 0.8 years (incidence 5.7% [95% CI 2.65%-10.6%]. There was one reported malignancy amongst 77 control patients (median duration of follow-up 0.8 years; incidence 1.3% [95% CI 0.03%-7.0%]). The majority of the malignancies developed in the lung or head and neck.

A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age (see section 4.4).

In addition, post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with infliximab with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, and most of whom were adolescent or young adult males (see section 4.4).

Heart failure

In a Phase II study aimed at evaluating infliximab in CHF, higher incidence of mortality due to worsening of heart failure were seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this study 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction ≤35%) were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Hepatobiliary events

In clinical studies, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury. Elevations of ALT ≥5 x Upper Limit of Normal (ULN) have been observed (see Table 2). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of infliximab, or modification of concomitant therapy. In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4).

**Table 2**
**Proportion of patients with increased ALT activity in clinical studies**

| Indication | Number of patients[3] | | Median follow-up (wks)[4] | | ≥3 x ULN | | ≥5 x ULN | |
|---|---|---|---|---|---|---|---|---|
| | placebo | infliximab | placebo | infliximab | placebo | infliximab | placebo | infliximab |
| Rheumatoid arthritis[1] | 375 | 1,087 | 58.1 | 58.3 | 3.2% | 3.9% | 0.8% | 0.9% |
| Crohn's disease[2] | 324 | 1,034 | 53.7 | 54.0 | 2.2% | 4.9% | 0.0% | 1.5% |
| Paediatric Crohn's disease | N/A | 139 | N/A | 53.0 | N/A | 4.4% | N/A | 1.5% |
| Ulcerative colitis | 242 | 482 | 30.1 | 30.8 | 1.2% | 2.5% | 0.4% | 0.6% |
| Paediatric Ulcerative colitis | N/A | 60 | N/A | 49.4 | N/A | 6.7% | N/A | 1.7% |
| Ankylosing spondylitis | 76 | 275 | 24.1 | 101.9 | 0.0% | 9.5% | 0.0% | 3.6% |
| Psoriatic arthritis | 98 | 191 | 18.1 | 39.1 | 0.0% | 6.8% | 0.0% | 2.1% |
| Plaque psoriasis | 281 | 1,175 | 16.1 | 50.1 | 0.4% | 7.7% | 0.0% | 3.4% |

1 Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
2 Placebo patients in the 2 Phase III studies in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomised to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day as active control in addition to placebo infliximab infusions.
3 Number of patients evaluated for ALT.
4 Median follow-up is based on patients treated.

Antinuclear antibodies (ANA)/Anti-double-stranded DNA (dsDNA) antibodies

Approximately half of infliximab-treated patients in clinical studies who were ANA negative at baseline developed a positive ANA during the study compared with approximately one fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of infliximab-treated patients compared with 0% of placebo-treated patients. At the last evaluation, 57% of infliximab-treated patients remained anti-dsDNA positive. Reports of lupus and lupus-like syndromes, however, remain uncommon (see section 4.4).

Paediatric population

*Juvenile rheumatoid arthritis patients*

Infliximab was studied in a clinical study in 120 patients (age range: 4-17 years old) with active juvenile rheumatoid arthritis despite methotrexate. Patients received 3 or 6 mg/kg infliximab as a 3-dose induction regimen (weeks 0, 2, 6 or weeks 14, 16, 20, respectively) followed by maintenance therapy every 8 weeks, in combination with methotrexate.

*Infusion reactions*
Infusion reactions occurred in 35% of patients with juvenile rheumatoid arthritis receiving 3 mg/kg compared with 17.5% of patients receiving 6 mg/kg. In the 3 mg/kg infliximab group, 4 out of 60 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2

of which were among the serious infusion reactions). In the 6 mg/kg group, 2 out of 57 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction (see section 4.4).

*Immunogenicity*
Antibodies to infliximab developed in 38% of patients receiving 3 mg/kg compared with 12% of patients receiving 6 mg/kg. The antibody titres were notably higher for the 3 mg/kg compared to the 6 mg/kg group.

*Infections*
Infections occurred in 68% (41/60) of children receiving 3 mg/kg over 52 weeks, 65% (37/57) of children receiving infliximab 6 mg/kg over 38 weeks and 47% (28/60) of children receiving placebo over 14 weeks (see section 4.4).

*Paediatric Crohn's disease patients*

The following adverse reactions were reported more commonly in paediatric Crohn's disease patients in the REACH study (see section 5.1) than in adult Crohn's disease patients: anaemia (10.7%), blood in stool (9.7%), leukopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%). In addition, bone fracture (6.8%) was reported, however, a causal association has not been established. Other special considerations are discussed below.

*Infusion-related reactions*
In REACH, 17.5% of randomised patients experienced 1 or more infusion reactions. There were no serious infusion reactions, and 2 subjects in REACH had non-serious anaphylactic reactions.

*Immunogenicity*
Antibodies to infliximab were detected in 3 (2.9%) paediatric patients.

*Infections*
In the REACH study, infections were reported in 56.3% of randomised subjects treated with infliximab. Infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Three cases of pneumonia (1 serious) and 2 cases of herpes zoster (both non-serious) were reported.

*Paediatric ulcerative colitis patients*

Overall, the adverse reactions reported in the paediatric ulcerative colitis trial (C0168T72) and adult ulcerative colitis (ACT 1 and ACT 2) studies were generally consistent. In C0168T72, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache. The most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on the q12 week vs. the q8 week dosing regimen.

*Infusion-related reactions*
Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the q8 week and 3 of 23 (13.0%) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

*Immunogenicity*
Antibodies to infliximab were detected in 4 (7.7%) patients through week 54.

*Infections*
Infections were reported in 31 (51.7%) of 60 treated patients in C0168T72 and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in C0168T72 was

similar to that in the paediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). The overall incidence of infections in C0168T72 was 13/22 (59%) in the every 8 week maintenance treatment group and 14/23 (60.9%) in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%]) vs.15/60 [25.0%]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups. Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

Post-marketing experience

Post-marketing spontaneous serious adverse reactions with infliximab in the paediatric population have included malignancies including hepatosplenic T-cell lymphomas, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive auto-antibodies (see sections 4.4 and 4.8).

Other special populations

*Elderly*

In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in infliximab plus methotrexate-treated patients 65 years and older (11.3%) than in those under 65 years of age (4.6%). In patients treated with methotrexate alone, the incidence of serious infections was 5.2% in patients 65 years and older compared to 2.7% in patients under 65 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

No case of overdose has been reported. Single doses up to 20 mg/kg have been administered without toxic effects.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, tumour necrosis factor alpha ($TNF_{\alpha}$) inhibitors, ATC code: L04AB02

Remsima is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency https://www.ema.europa.eu.

Mechanism of action

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both

soluble and transmembrane forms of $TNF_{\alpha}$ but not to lymphotoxin α ($TNF_{\beta}$).

Pharmacodynamic effects

Infliximab inhibits the functional activity of $TNF_{\alpha}$ in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human $TNF_{\alpha}$ and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human $TNF_{\alpha}$, a process that parallels the loss of $TNF_{\alpha}$ bioactivity.

Elevated concentrations of $TNF_{\alpha}$ have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP), and increased haemoglobin levels in rheumatoid arthritis patients with reduced haemoglobin levels, compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalisation of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, short term treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin.

Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable $TNF_{\alpha}$. Infliximab treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, CRP. Total peripheral white blood cell counts were minimally affected in infliximab-treated patients, although changes in lymphocytes, monocytes and neutrophils reflected shifts towards normal ranges. Peripheral blood mononuclear cells (PBMC) from infliximab-treated patients showed undiminished proliferative responsiveness to stimuli compared with untreated patients, and no substantial changes in cytokine production by stimulated PBMC were observed following treatment with infliximab. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that infliximab treatment caused a reduction in the number of cells capable of expressing $TNF_{\alpha}$ and interferon γ. Additional histological studies provided evidence that treatment with infliximab reduces the infiltration of inflammatory cells into affected areas of the intestine and the presence of inflammation markers at these sites. Endoscopic studies of intestinal mucosa have shown evidence of mucosal healing in infliximab-treated patients.

Clinical efficacy and safety

*Adult rheumatoid arthritis*

The efficacy of infliximab was assessed in two multicentre, randomised, double-blind, pivotal clinical studies: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of the following 5 criteria: (1) evaluator's global assessment, (2) patient's global assessment, (3) functional/disability measure, (4) visual analogue pain scale and (5) erythrocyte sedimentation rate or C-reactive protein. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percent improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the

total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function.

The ATTRACT study evaluated responses at 30, 54 and 102 weeks in a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter. All patients were on stable methotrexate doses (median 15 mg/wk) for 6 months prior to enrolment and were to remain on stable doses throughout the study.

Results from week 54 (ACR20, total van der Heijde-modified Sharp score and HAQ) are shown in Table 3. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 3).

The effects observed at 54 weeks were maintained through 102 weeks. Due to a number of treatment withdrawals, the magnitude of the effect difference between infliximab and the methotrexate alone group cannot be defined.

**Table 3**
**Effects on ACR20, Structural Joint Damage and Physical Function at week 54, ATTRACT**

| | | Infliximab[b] | | | | |
|---|---|---|---|---|---|---|
| | Control[a] | 3 mg/kg q 8 wks | 3 mg/kg q 4 wks | 10 mg/kg q 8 wks | 10 mg/kg q 4 wks | All infliximab[b] |
| Patients with ACR20 response/Patients evaluated (%) | 15/88 (17%) | 36/86 (42%) | 41/86 (48%) | 51/87 (59%) | 48/81 (59%) | 176/340 (52%) |
| Total score[d] (van der Heijde-modified Sharp score) | | | | | | |
| Change from baseline (Mean ± SD[c]) | 7.0 ± 10.3 | 1.3 ± 6.0 | 1.6 ± 8.5 | 0.2 ± 3.6 | -0.7 ± 3.8 | 0.6 ± 5.9 |
| Median (Interquartile range) | 4.0 (0.5,9.7) | 0.5 (-1.5,3.0) | 0.1 (-2.5,3.0) | 0.5 (-1.5,2.0) | -0.5 (-3.0,1.5) | 0.0 (-1.8,2.0) |

| | | Infliximab[b] | | | | |
|---|---|---|---|---|---|---|
| | Control[a] | 3 mg/kg q 8 wks | 3 mg/kg q 4 wks | 10 mg/kg q 8 wks | 10 mg/kg q 4 wks | All infliximab[b] |
| Patients with no deterioration/patients evaluated (%)[c] | 13/64 (20%) | 34/71 (48%) | 35/71 (49%) | 37/77 (48%) | 44/66 (67%) | 150/285 (53%) |
| HAQ change from baseline over time[e] (patients evaluated) | 87 | 86 | 85 | 87 | 81 | 339 |
| Mean ± SD[c] | 0.2 ± 0.3 | 0.4 ± 0.3 | 0.5 ± 0.4 | 0.5 ± 0.5 | 0.4 ± 0.4 | 0.4 ± 0.4 |

a control = All patients had active RA despite treatment with stable methotrexate doses for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤10 mg/day) and/or NSAIDs was permitted, and folate supplementation was given.
b all infliximab doses given in combination with methotrexate and folate with some on corticosteroids and/or NSAIDs
c p <0.001, for each infliximab treatment group vs. control
d greater values indicate more joint damage.
eHAQ = Health Assessment Questionnaire; greater values indicate less disability.

The ASPIRE study evaluated responses at 54 weeks in 1,004 methotrexate naive patients with early (≤3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (optimised to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from week 54 are shown in Table 4.

After 54 weeks of treatment, both doses of infliximab + methotrexate resulted in statistically significantly greater improvement in signs and symptoms compared to methotrexate alone as measured by the proportion of patients achieving ACR20, 50 and 70 responses.

In ASPIRE, more than 90% of patients had at least two evaluable X-rays. Reduction in the rate of progression of structural damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone.

**Table 4**
**Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE**

| | | Infliximab + MTX | | |
|---|---|---|---|---|
| | Placebo + MTX | 3 mg/kg | 6 mg/kg | Combined |
| Subjects randomised | 282 | 359 | 363 | 722 |
| Percentage ACR improvement | | | | |
| Mean ± SD[a] | 24.8 ± 59.7 | 37.3 ± 52.8 | 42.0 ± 47.3 | 39.6 ± 50.1 |
| Change from baseline in total van der Heijde-modified Sharp score[b] | | | | |
| Mean ± SD[a] | 3.70 ± 9.61 | 0.42 ± 5.82 | 0.51 ± 5.55 | 0.46 ± 5.68 |
| Median | 0.43 | 0.00 | 0.00 | 0.00 |
| Improvement from baseline in HAQ averaged over time from week 30 to week 54[c] | | | | |
| Mean ± SD[d] | 0.68 ± 0.63 | 0.80 ± 0.65 | 0.88 ± 0.65 | 0.84 ± 0.65 |

a p <0.001, for each infliximab treatment group vs control.
b greater values indicate more joint damage.
c HAQ = Health Assessment Questionnaire; greater values indicate less disability.
d p = 0.030 and <0.001 for the 3 mg/kg and 6 mg/kg treatment groups respectively vs. placebo + MTX.

Data to support dose titration in rheumatoid arthritis come from ATTRACT, ASPIRE and the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the study arms (group 2, n=329), patients with an inadequate response were allowed to dose titrate with 1.5 mg/kg increments from 3 up to 9 mg/kg. The majority (67%) of these patients did not require any dose titration. Of the patients who required a dose titration, 80% achieved clinical response and the majority (64%) of these required only one adjustment of 1.5 mg/kg.

*Adult Crohn's disease*

*Induction treatment in moderately to severely active Crohn's disease*
The efficacy of a single dose treatment with infliximab was assessed in 108 patients with active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥220 ≤400) in a randomised, double-blinded, placebo-controlled, dose-response study. Of these 108 patients, 27 were treated with the recommended dosage of infliximab 5 mg/kg. All patients had experienced an inadequate response to prior conventional therapies. Concurrent use of stable doses of conventional therapies was permitted, and 92% of patients continued to receive these therapies.

The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥70 points from baseline at the 4-week evaluation and without an increase in the use of medicinal products or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients in clinical remission at week 4 (CDAI <150) and clinical response over time.

At week 4, following administration of a single dose, 22/27 (81%) of infliximab-treated patients receiving a 5 mg/kg dose achieved a clinical response vs. 4/25 (16%) of the placebo-treated patients ($p < 0.001$). Also at week 4, 13/27 (48%) of infliximab-treated patients achieved a clinical remission (CDAI <150) vs. 1/25 (4%) of placebo-treated patients. A response was observed within 2 weeks, with a maximum response at 4 weeks. At the last observation at 12 weeks, 13/27 (48%) of infliximab-treated patients were still responding.

*Maintenance treatment in moderately to severely active Crohn's disease in adults*
The efficacy of repeated infusions with infliximab was studied in a 1-year clinical study (ACCENT I). A total of 573 patients with moderately to severely active Crohn's disease (CDAI ≥220 ≤400) received a single infusion of 5 mg/kg at week 0. 178 of the 580 enrolled patients (30.7%) were defined as having severe disease (CDAI score > 300 and concomitant corticosteroid and/or immunosuppressants) corresponding to the population defined in the indication (see section 4.1). At week 2, all patients were assessed for clinical response and randomised to one of 3 treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group. All 3 groups received repeated infusions at week 2, 6 and every 8 weeks thereafter.

Of the 573 patients randomised, 335 (58%) achieved clinical response by week 2. These patients were classified as week-2 responders and were included in the primary analysis (see Table 5). Among patients classified as non-responders at week 2, 32% (26/81) in the placebo maintenance group and 42% (68/163) in the infliximab group achieved clinical response by week 6. There was no difference between groups in the number of late responders thereafter.

The co-primary endpoints were the proportion of patients in clinical remission (CDAI <150) at week 30 and time to loss of response through week 54. Corticosteroid tapering was permitted after week 6.

**Table 5**
**Effects on response and remission rate, data from ACCENT I (Week-2 responders)**

| | ACCENT I (Week-2 responders) % of patients | | |
|---|---|---|---|
| | Placebo Maintenance (n=110) | Infliximab Maintenance 5 mg/kg (n=113) (p value) | Infliximab Maintenance 10 mg/kg (n=112) (p value) |
| Median time to loss of response through week 54 | 19 weeks | 38 weeks (0.002) | >54 weeks (<0.001) |
| **Week 30** | | | |
| Clinical Response[a] | 27.3 | 51.3 (<0.001) | 59.1 (<0.001) |
| Clinical Remission | 20.9 | 38.9 (0.003) | 45.5 (<0.001) |
| Steroid-Free Remission | 10.7 (6/56) | 31.0 (18/58) (0.008) | 36.8 (21/57) (0.001) |
| **Week 54** | | | |
| Clinical Response[a] | 15.5 | 38.1 (<0.001) | 47.7 (<0.001) |
| Clinical Remission | 13.6 | 28.3 (0.007) | 38.4 (<0.001) |
| Sustained Steroid-Free Remission[b] | 5.7 (3/53) | 17.9 (10/56) (0.075) | 28.6 (16/56) (0.002) |

a Reduction in CDAI ≥25% and ≥70 points.
b CDAI <150 at both Week 30 and 54 and not receiving corticosteroids in the 3 months prior to Week 54 among patients who were receiving corticosteroids at baseline.

Beginning at week 14, patients who had responded to treatment, but subsequently lost their clinical benefit, were allowed to cross over to a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Eighty nine percent (50/56) of patients who lost clinical response on infliximab 5 mg/kg maintenance therapy after week 14 responded to treatment with infliximab 10 mg/kg.

Improvements in quality of life measures, a reduction in disease-related hospitalisations and corticosteroid use were seen in the infliximab maintenance groups compared with the placebo maintenance group at weeks 30 and 54.

Infliximab with or without AZA was assessed in a randomised, double-blind, active comparator study (SONIC) of 508 adult patients with moderate to severe Crohn's disease (CDAI ≥220 ≤450) who were naive to biologics and immunosuppressants and had a median disease duration of 2.3 years. At baseline 27.4% of patients were receiving systemic corticosteroids, 14.2% of patients were receiving budesonide, and 54.3% of patients were receiving 5-ASA compounds. Patients were randomised to receive AZA monotherapy, infliximab monotherapy, or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily.

The primary endpoint of the study was corticosteroid-free clinical remission at week 26, defined as patients in clinical remission (CDAI of <150) who, for at least 3 weeks, had not taken oral systemic corticosteroids (prednisone or equivalent) or budesonide at a dose >6 mg/day. For results see Table 6. The proportions of patients with mucosal healing at week 26 were significantly greater in the infliximab plus AZA combination (43.9%, p<0.001) and infliximab monotherapy groups (30.1%, p=0.023) compared to the AZA monotherapy group (16.5%).

**Table 6**
**Percent of patients achieving corticosteroid-free clinical remission at Week 26, SONIC**

| | AZA Monotherapy | Infliximab Monotherapy | Infliximab + AZA Combination therapy |
|---|---|---|---|
| **Week 26** | | | |
| All randomised patients | 30.0% (51/170) | 44.4% (75/169) (p=0.006)* | 56.8% (96/169) (p<0.001)* |

* p-values represent each infliximab treatment group vs. AZA monotherapy.

Similar trends in the achievement of corticosteroid-free clinical remission were observed at week 50. Furthermore, improved quality of life as measured by IBDQ was observed with infliximab.

*Induction treatment in fistulising active Crohn's disease*
The efficacy was assessed in a randomised, double-blinded, placebo-controlled study in 94 patients with fistulising Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty one of these patients were treated with infliximab 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these therapies. Patients received three doses of either placebo or infliximab at weeks 0, 2 and 6. Patients were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistulae draining upon gentle compression on at least two consecutive visits (4 weeks apart), without an increase in the use of medicinal products or surgery for Crohn's disease.

Sixty eight percent (21/31) of infliximab-treated patients receiving a 5 mg/kg dose regimen achieved a clinical response vs. 26% (8/31) placebo-treated patients (p=0.002). The median time to onset of response in the infliximab-treated group was 2 weeks. The median duration of response was 12 weeks. Additionally, closure of all fistulae was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients (p=0.001).

*Maintenance treatment in fistulising active Crohn's disease*
The efficacy of repeated infusions with infliximab in patients with fistulising Crohn's disease was studied in a 1-year clinical study (ACCENT II). A total of 306 patients received 3 doses of infliximab 5 mg/kg at week 0, 2 and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. At week 14, 282 patients were assessed for clinical response and randomised to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46.

Week-14 responders (195/282) were analysed for the primary endpoint, which was time from randomisation to loss of response (see Table 7). Corticosteroid tapering was permitted after week 6.

**Table 7**
**Effects on response rate, data from ACCENT II (Week-14 responders)**

| | ACCENT II (Week-14 responders) | | |
|---|---|---|---|
| | Placebo Maintenance (n=99) | Infliximab Maintenance (5 mg/kg) (n=96) | p-value |
| Median time to loss of response through week 54 | 14 weeks | >40 weeks | <0.001 |
| **Week 54** | | | |
| Fistula Response (%)[a] | 23.5 | 46.2 | 0.001 |
| Complete fistula response (%)[b] | 19.4 | 36.3 | 0.009 |

a A ≥50% reduction from baseline in the number of draining fistulas over a period of ≥4 weeks.
b Absence of any draining fistulas.

Beginning at week 22, patients who initially responded to treatment and subsequently lost their response were eligible to cross over to active re-treatment every 8 weeks at a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Among patients in the infliximab 5 mg/kg group who crossed over because of loss of fistula response after week 22, 57% (12/21) responded to re-treatment with infliximab 10 mg/kg every 8 weeks.

There was no significant difference between placebo and infliximab for the proportion of patients with sustained closure of all fistulas through week 54, for symptoms such as proctalgia, abscesses and urinary tract infection or for number of newly developed fistulas during treatment.

Maintenance therapy with infliximab every 8 weeks significantly reduced disease-related hospitalisations and surgeries compared with placebo. Furthermore, a reduction in corticosteroid use and improvements in quality of life were observed.

*Adult ulcerative colitis*

The safety and efficacy of infliximab were assessed in two (ACT 1 and ACT 2) randomised, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥2) with an inadequate response to conventional therapies [oral corticosteroids, aminosalicylates and/or immunomodulators (6-MP, AZA)]. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In both studies, patients were randomised to receive either placebo, 5 mg/kg infliximab, or 10 mg/kg infliximab at weeks 0, 2, 6, 14 and 22, and in ACT 1 at weeks 30, 38 and 46. Corticosteroid taper was permitted after week 8.

**Table 8**
**Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2**

| | | Infliximab | | |
|---|---|---|---|---|
| | Placebo | 5 mg/kg | 10 mg/kg | Combined |
| Subjects randomised | 244 | 242 | 242 | 484 |
| **Percentage of subjects in clinical response and in sustained clinical response** | | | | |
| Clinical response at Week 8[a] | 33.2% | 66.9% | 65.3% | 66.1% |
| Clinical response at Week 30[a] | 27.9% | 49.6% | 55.4% | 52.5% |
| Sustained response (clinical response at both Week 8 and Week 30)[a] | 19.3% | 45.0% | 49.6% | 47.3% |
| **Percentage of subjects in clinical remission and sustained remission** | | | | |
| Clinical remission at Week 8[a] | 10.2% | 36.4% | 29.8% | 33.1% |
| Clinical remission at Week 30[a] | 13.1% | 29.8% | 36.4% | 33.1% |
| Sustained remission(in remission at both Week 8 and Week 30)[a] | 5.3% | 19.0% | 24.4% | 21.7% |
| **Percentage of subjects with mucosal healing** | | | | |
| Mucosal healing at Week 8[a] | 32.4% | 61.2% | 60.3% | 60.7% |
| Mucosal healing at Week 30[a] | 27.5% | 48.3% | 52.9% | 50.6% |

a $p < 0.001$, for each infliximab treatment group vs. placebo.

The efficacy of infliximab through week 54 was assessed in the ACT 1 study.
At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p<0.001$). Clinical remission and mucosal healing occurred in a greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.6% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportions of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in the placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

A greater proportion of patients in the combined infliximab treatment group were able to discontinue corticosteroids while remaining in clinical remission compared to the placebo treatment group at both week 30 (22.3% vs. 7.2%, p <0.001, pooled ACT 1 & ACT 2 data) and week 54 (21.0% vs. 8.9%, p=0.022, ACT 1 data).

The pooled data analysis from the ACT 1 and ACT 2 studies and their extensions, analysed from baseline through 54 weeks, demonstrated a reduction of ulcerative colitis-related hospitalisations and surgical procedures with infliximab treatment. The number of ulcerative colitis-related hospitalisations was significantly lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of hospitalisations per 100 subject-years: 21 and 19 vs. 40 in the placebo group; p=0.019 and p=0.007, respectively). The number of ulcerative colitis-related surgical procedures was also lower in the 5 and 10 mg/kg infliximab treatment groups than in the placebo group (mean number of surgical procedures per 100 subject-years: 22 and 19 vs. 34*;* p=0.145 and p=0.022, respectively).

The proportion of subjects who underwent colectomy at any time within 54 weeks following the first infusion of study agent were collected and pooled from the ACT 1 and ACT 2 studies and their extensions. Fewer subjects underwent colectomy in the 5 mg/kg infliximab group (28/242 or 11.6% [N.S.]) and the 10 mg/kg infliximab group (18/242 or 7.4% [p=0.011]) than in the placebo group (36/244; 14.8%).

The reduction in incidence of colectomy was also examined in another randomised, double-blind study (C0168Y06) in hospitalised patients (n=45) with moderately to severely active ulcerative colitis who failed to respond to intravenous corticosteroids and who were therefore at higher risk for colectomy. Significantly fewer colectomies occurred within 3 months of study infusion in patients who received a single dose of 5 mg/kg infliximab compared to patients who received placebo (29.2% vs. 66.7% respectively, p=0.017).

In ACT 1 and ACT 2, infliximab improved quality of life, confirmed by statistically significant improvement in both a disease specific measure, IBDQ, and by improvement in the generic 36-item short form survey SF-36.

*Adult ankylosing spondylitis*

Efficacy and safety of infliximab were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥ 4 and spinal pain ≥ 4 on a scale of 1-10).

In the first study (P01522), which had a 3 month double-blind phase, 70 patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). At week 12, placebo patients were switched to infliximab 5 mg/kg every 6 weeks up to week 54. After the first year of the study, 53 patients continued into an open-label extension to week 102.

In the second clinical study (ASSERT), 279 patients were randomised to receive either placebo (Group 1, n=78) or 5 mg/kg infliximab (Group 2, n=201) at 0, 2 and 6 weeks and every 6 weeks to week 24. Thereafter, all subjects continued on infliximab every 6 weeks to week 96. Group 1 received 5 mg/kg infliximab. In Group 2, starting with the week 36 infusion, patients who had a BASDAI ≥3 at 2 consecutive visits, received 7.5 mg/kg infliximab every 6 weeks thereafter through week 96.

In ASSERT, improvement in signs and symptoms was observed as early as week 2. At week 24, the number of ASAS 20 responders was 15/78 (19%) in the placebo group, and 123/201 (61%) in the 5 mg/kg infliximab group (p<0.001). There were 95 subjects from group 2 who continued on 5 mg/kg every 6 weeks. At 102 weeks there were 80 subjects still on infliximab treatment and among those, 71 (89%) were ASAS 20 responders.

In P01522, improvement in signs and symptoms was also observed as early as week 2. At week 12, the number of BASDAI 50 responders were 3/35 (9%) in the placebo group, and 20/35 (57%) in the 5 mg/kg group (p<0.01). There were 53 subjects who continued on 5 mg/kg every 6 weeks. At

102 weeks there were 49 subjects still on infliximab treatment and among those, 30 (61%) were BASDAI 50 responders.

In both studies, physical function and quality of life as measured by the BASFI and the physical component score of the SF-36 were also improved significantly.

*Adult psoriatic arthritis*

Efficacy and safety were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active psoriatic arthritis.

In the first clinical study (IMPACT), efficacy and safety of infliximab were studied in 104 patients with active polyarticular psoriatic arthritis. During the 16-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, and 14 (52 patients in each group). Starting at week 16, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 8 weeks up to week 46. After the first year of the study, 78 patients continued into an open-label extension to week 98.

In the second clinical study (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints). Forty six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, 47 placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46.

Key efficacy results for IMPACT and IMPACT 2 are shown in Table 9 below:

**Table 9**
**Effects on ACR and PASI in IMPACT and IMPACT 2**

| | IMPACT | | | IMPACT 2* | | |
|---|---|---|---|---|---|---|
| | Placebo (Week 16) | Infliximab (Week 16) | Infliximab (Week 98) | Placebo (Week 24) | Infliximab (Week 24) | Infliximab (Week 54) |
| Patients randomised | 52 | 52 | N/A[a] | 100 | 100 | 100 |
| ACR response (% of patients) N | 52 | 52 | 78 | 100 | 100 | 100 |
| ACR 20 response* | 5 (10%) | 34 (65%) | 48 (62%) | 16 (16%) | 54 (54%) | 53 (53%) |
| ACR 50 response* | 0 (0%) | 24 (46%) | 35 (45%) | 4 (4%) | 41 (41%) | 33 (33%) |
| ACR 70 response* | 0 (0%) | 15 (29%) | 27 (35%) | 2 (2%) | 27 (27%) | 20 (20%) |
| PASI response (% of patients)[b] N | | | | 87 | 83 | 82 |
| PASI 75 response** | | | | 1 (1%) | 50 (60%) | 40 (48.8%) |

* ITT-analysis where subjects with missing data were included as non-responders.
a Week 98 data for IMPACT includes combined placebo crossover and infliximab patients who entered the open-label extension.

b Based on patients with PASI >2.5 at baseline for IMPACT, and patients with >3% BSA psoriasis skin involvement at baseline in IMPACT 2.

** PASI 75 response for IMPACT not included due to low N; p<0.001 for infliximab vs. placebo at week 24 for IMPACT 2.

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54, respectively. Efficacy has been demonstrated with or without concomitant use of methotrexate. Decreases in parameters of peripheral activity characteristic of psoriatic arthritis (such as number of swollen joints, number of painful/tender joints, dactylitis and presence of enthesopathy) were seen in the infliximab-treated patients.

Radiographic changes were assessed in IMPACT 2. Radiographs of hands and feet were collected at baseline, weeks 24 and 54. Infliximab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at the week 24 primary endpoint as measured by change from baseline in total modified vdH-S score (mean ± SD score was 0.82 ± 2.62 in the placebo group compared with -0.70 ± 2.53 in the infliximab group; p<0.001). In the infliximab group, the mean change in total modified vdH-S score remained below 0 at the week 54 timepoint.

Infliximab-treated patients demonstrated significant improvement in physical function as assessed by HAQ. Significant improvements in health-related quality of life were also demonstrated as measured by the physical and mental component summary scores of the SF-36 in IMPACT 2.

*Adult psoriasis*

The efficacy of infliximab was assessed in two multicentre, randomised, double-blind studies: SPIRIT and EXPRESS. Patients in both studies had plaque psoriasis (Body Surface Area [BSA] ≥10% and Psoriasis Area and Severity Index [PASI] score ≥12). The primary endpoint in both studies was the percent of patients who achieved ≥75% improvement in PASI from baseline at week 10.

SPIRIT evaluated the efficacy of infliximab induction therapy in 249 patients with plaque psoriasis that had previously received PUVA or systemic therapy. Patients received either 3 or 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6. Patients with a PGA score ≥3 were eligible to receive an additional infusion of the same treatment at week 26.
In SPIRIT, the proportion of patients achieving PASI 75 at week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group (p<0.001). By week 26, twenty weeks after the last induction dose, 30% of patients in the 5 mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of >20 weeks. No rebound was observed.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis. Patients received 5 mg/kg infliximab- or placebo-infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8 weeks through week 22 in the placebo group and through week 46 in the infliximab group. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg). Nail psoriasis was assessed using the Nail Psoriasis Severity Index (NAPSI). Prior therapy with PUVA, methotrexate, ciclosporin, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in Table 10. In infliximab treated subjects, significant PASI 50 responses were apparent at the first visit (week 2) and PASI 75 responses by the second visit (week 6). Efficacy was similar in the subgroup of patients that were exposed to previous systemic therapies compared to the overall study population.

**Table 10**
**Summary of PASI response, PGA response and percent of patients with all nails cleared at Weeks 10, 24 and 50. EXPRESS**

| | Placebo → Infliximab 5 mg/kg (at week 24) | Infliximab 5 mg/kg |
|---|---|---|
| **Week 10** | | |
| N | 77 | 301 |
| ≥90% improvement | 1 (1.3%) | 172 (57.1%) [a] |
| ≥75% improvement | 2 (2.6%) | 242 (80.4%) [a] |
| ≥50% improvement | 6 (7.8%) | 274 (91.0%) |
| PGA of cleared (0) or minimal (1) | 3 (3.9%) | 242 (82.9%) [ab] |
| PGA of cleared (0), minimal (1), or mild (2) | 14 (18.2%) | 275 (94.2%) [ab] |
| **Week 24** | | |
| N | 77 | 276 |
| ≥90% improvement | 1 (1.3%) | 161 (58.3%) [a] |
| ≥75% improvement | 3 (3.9%) | 227 (82.2%) [a] |
| ≥50% improvement | 5 (6.5%) | 248 (89.9%) |
| PGA of cleared (0) or minimal (1) | 2 (2.6%) | 203 (73.6%) [a] |
| PGA of cleared (0), minimal (1), or mild (2) | 15 (19.5%) | 246 (89.1%) [a] |
| **Week 50** | | |
| N | 68 | 281 |
| ≥90% improvement | 34 (50.0%) | 127 (45.2%) |
| ≥75% improvement | 52 (76.5%) | 170 (60.5%) |
| ≥50% improvement | 61 (89.7%) | 193 (68.7%) |
| PGA of cleared (0) or minimal (1) | 46 (67.6%) | 149 (53.0%) |
| PGA of cleared (0), minimal (1), or mild (2) | 59 (86.8%) | 189 (67.3%) |
| **All nails cleared[c]** | | |
| Week 10 | 1/65(1.5%) | 16/235 (6.8%) |
| Week 24 | 3/65 (4.6%) | 58/223 (26.0%) [a] |
| Week 50 | 27/64 (42.2%) | 92/226 (40.7%) |

a $p < 0.001$, for each infliximab treatment group vs. control.
b n = 292.
c Analysis was based on subjects with nail psoriasis at baseline (81.8% of subjects). Mean baseline NAPSI scores were 4.6 and 4.3 in infliximab and placebo group.

Significant improvements from baseline were demonstrated in DLQI ($p<0.001$) and the physical and mental component scores of the SF 36 ($p<0.001$ for each component comparison).

Paediatric population

*Paediatric Crohn's disease (6 to 17 years)*

In the REACH study, 112 patients (6 to 17 years, median age 13.0 years) with moderate to severe, active Crohn's disease (median paediatric CDAI of 40) and an inadequate response to conventional therapies were to receive 5 mg/kg infliximab at weeks 0, 2, and 6. All patients were required to be on a stable dose of 6-MP, AZA or MTX (35% were also receiving corticosteroids at baseline). Patients assessed by the investigator to be in clinical response at week 10 were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose (10 mg/kg) and/or shorter dosing interval (q8 weeks) was allowed. Thirty two (32) evaluable paediatric patients crossed over (9 subjects in the q8 weeks and 23 subjects in the q12 weeks maintenance groups). Twenty four of these patients (75.0%) regained clinical response after crossing over.

The proportion of subjects in clinical response at week 10 was 88.4% (99/112). The proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112).
At week 30, the proportion of subjects in clinical remission was higher in the q8 week (59.6%, 31/52) than the q12 week maintenance treatment group (35.3%, 18/51; p=0.013). At week 54, the figures were 55.8% (29/52) and 23.5% (12/51) in the q8 weeks and q12 weeks maintenance groups, respectively ($p < 0.001$).
Data about fistulas were derived from PCDAI scores. Of the 22 subjects that had fistulas at baseline, 63.6% (14/22), 59.1% (13/22) and 68.2% (15/22) were in complete fistula response at week 10, 30 and 54, respectively, in the combined q8 weeks and q12 weeks maintenance groups.

In addition, statistically and clinically significant improvements in quality of life and height, as well as a significant reduction in corticosteroid use, were observed versus baseline.

*Paediatric ulcerative colitis (6 to 17 years)*

The safety and efficacy of infliximab were assessed in a multicentre, randomised, open-label, parallel-group clinical study (C0168T72) in 60 paediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; endoscopic subscore ≥ 2) with an inadequate response to conventional therapies. At baseline 53% of patients were receiving immunomodulator therapy (6-MP, AZA and/or MTX) and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after week 0.

All patients received an induction regimen of 5 mg/kg infliximab at weeks 0, 2, and 6. Patients who did not respond to infliximab at week 8 (n=15) received no further medicinal product and returned for safety follow-up. At week 8, 45 patients were randomised and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen.

The proportion of patients in clinical response at week 8 was 73.3% (44/60). Clinical response at week 8 was similar between those with or without concomitant immunomodulator use at baseline. Clinical remission at week 8 was 33.3% (17/51) as measured by the Paediatric Ulcerative Colitis Activity Index (PUCAI) score.

At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance group and 18% (4/22) in the q12 week maintenance treatment group. For patients receiving corticosteroids at baseline, the proportion of patients in remission and not receiving corticosteroids at week 54 was 38.5% (5/13) for the q8 week and 0% (0/13) for the q12 week maintenance treatment group.

In this study, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 vs.15/60). While the numbers of patients in each subgroup are too small to draw definitive conclusions about the effect of age, there was a higher number of patients in the younger age group who stepped up in dose or discontinued treatment due to inadequate efficacy.

*Other paediatric indications*

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing infliximab in all subsets of the paediatric population in rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis and Crohn's disease (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration ($C_{max}$) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median $V_d$ of 3.0 to 4.1 litres) was not dependent

on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. No time-dependency of the Pharmacokinetics was observed. The elimination pathways for infliximab have not been characterised. Unchanged infliximab was not detected in urine. No major age- or weight-related differences in clearance or volume of distribution were observed in rheumatoid arthritis patients. The pharmacokinetics of infliximab in elderly patients has not been studied. Studies have not been performed in patients with liver or renal disease.

At single doses of 3, 5, or 10 mg/kg, the median $C_{max}$ values were 77, 118 and 277 micrograms/mL, respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after the recommended single dose of 5 mg/kg for Crohn's disease and the rheumatoid arthritis maintenance dose of 3 mg/kg every 8 weeks.

Repeated administration of infliximab (5 mg/kg at 0, 2 and 6 weeks in fistulising Crohn's disease, 3 or 10 mg/kg every 4 or 8 weeks in rheumatoid arthritis) resulted in a slight accumulation of infliximab in serum after the second dose. No further clinically relevant accumulation was observed. In most fistulising Crohn's disease patients, infliximab was detected in serum for 12 weeks (range 4-28 weeks) after administration of the regimen.

Paediatric population

Population pharmacokinetic analysis based on data obtained from patients with ulcerative colitis (N=60), Crohn's disease (N=112), juvenile rheumatoid arthritis (N=117) and Kawasaki disease (N=16) with an overall age range from 2 months to 17 years indicated that exposure to infliximab was dependent on body weight in a non-linear way. Following administration of 5 mg/kg infliximab every 8 weeks, the predicted median steady-state infliximab exposure (area under concentration-time curve at steady state, AUCss) in paediatric patients aged 6 years to 17 years was approximately 20% lower than the predicted median steady-state medicinal product exposure in adults. The median AUCss in paediatric patients aged 2 years to less than 6 years was predicted to be approximately 40% lower than that in adults, although the number of patients supporting this estimate is limited.

### 5.3 Preclinical safety data

Infliximab does not cross react with $TNF_{\alpha}$ from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse $TNF_{\alpha}$, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse $TNF_{\alpha}$, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.

Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in $TNF_{\alpha}$ demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Acetic acid
Sodium acetate trihydrate
Sorbitol (E420)
Polysorbate 80 (E433)
Water for injections

## 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## 6.3 Shelf life

Before dilution: 4 years at 2°C – 8°C.

Remsima may be stored at temperatures up to a maximum of 30°C for a single period of up to 15 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Remsima must not be returned to refrigerated storage.

After dilution:
Chemical and physical in use stability of the diluted solution has been demonstrated for up to 60 days at 2 °C to 8 °C and for an additional 24 hours at 30°C after removal from refrigeration. From a microbiological point of view, the infusion solution should be administered immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has been taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions up to 30°C before dilution of the medicinal product, see section 6.3.

For storage conditions after dilution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Type 1 glass vial with a (butyl) rubber stopper and an aluminium seal with a flip-off button.

Pack sizes of 1, 2, 3, 4, 5 vials.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

1. The dose and the number of Remsima vials have to be calculated. Each Remsima vial contains either 100 mg or 350 mg infliximab. The required total volume of Remsima concentrate has to be calculated.

2. The required volume of the Remsima concentrate should be diluted to 250 mL with sodium chloride 9 mg/mL (0.9%) solution for infusion. Do not dilute the Remsima concentrate with any other diluent. The dilution can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250 mL glass bottle or infusion bag equal to the required volume of Remsima concentrate. The required volume of Remsima concentrate should slowly be added to the 250-mL infusion bottle or bag and gently be mixed. For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL, 1000 mL) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/mL. If stored refrigerated after dilution, the infusion solution must be allowed to equilibrate at room temperature (up to 30°C) for 3 hours prior to Step 3 (infusion).

3. The infusion solution has to be administered over a period of not less than the infusion time recommended (see section 4.2). Only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometre or less) should be used. Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has been taken place in controlled and validated aseptic conditions (see section 6.3 above). Any unused portion of the infusion solution should not be stored for reuse.

4. Remsima should be visually inspected for particulate matter or discolouration prior to administration. If visibly opaque particles, discolouration or foreign particles are observed it should not be used.

5. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/018
EU/1/13/853/019
EU/1/13/853/020
EU/1/13/853/021
EU/1/13/853/022
EU/1/13/853/023
EU/1/13/853/024
EU/1/13/853/025
EU/1/13/853/026
EU/1/13/853/027

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: DD Month YYYY
Date of latest renewal: DD Month YYYY

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

CELLTRION, Inc.
23, Academy-ro,
Yeonsu-gu, Incheon, 22014
Republic of Korea

CELLTRION, Inc. (Plant II, CLT2)
20, Academy-ro 51 beon-gil,
Yeonsu-gu, Incheon, 22014
Republic of Korea

Lonza Biologics Tuas Pte Ltd
35 Tuas South Avenue 6,
Singapore 637377, Singapore

Name and address of the manufacturer responsible for batch release

Millmount Healthcare Ltd.
Block 7
City North Business Campus
Stamullen, Co. Meath K32 YD60
Ireland

Nuvisan GmbH
Wegenerstraße 13,
89231 Neu-Ulm,
Germany

Nuvisan France SARL
2400, Route des Colles,
06410, Biot,
France

Kymos, SL
Ronda De Can Fatjó 7B, Parc Tecnològic del Vallès,
Cerdanyola del Vallès,
Barcelona, 08290,
Spain

Midas Pharma GmbH
Rheinstraße 49
55218 Ingelheim am Rhein
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The educational programme consists of a patient reminder card to be held by the patient. The card is aimed at both serving as a reminder to record the dates and outcomes of specific tests and to facilitate the patient sharing of special information with healthcare professionals(s) (HCPs) treating the patient about on-going treatment with the product.

**The patient reminder card** shall contain the following key messages:

- A reminder to patients to show the patient reminder card to all treating HCPs, including in conditions of emergency, and a message for HCPs that the patient is using Remsima
- A statement that the brand name and batch number should be recorded
- Provision to record the type, date, and result of TB screenings
- That treatment with Remsima may increase the risks of serious infections/sepsis, opportunistic infections, tuberculosis, hepatitis B reactivation, and BCG breakthrough in infants with *in utero* or breast-feeding exposure to infliximab, and when to seek attention from a HCP
- That Remsima 100 mg and 350 mg concentrate for solution for infusion contains sorbitol and if the patient has hereditary fructose intolerance, this intravenously administered formulation should not be used.
- Contact details of the prescriber

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 100 mg powder for concentrate for solution for infusion
infliximab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 100 mg of infliximab.
After reconstitution one ml contains 10 mg of infliximab.

## 3. LIST OF EXCIPIENTS

Excipients: sucrose, polysorbate 80, sodium dihydrogen phosphate monohydrate, disodium phosphate dihydrate.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.

1 vial
2 vials
3 vials
4 vials
5 vials

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

Reconstitute and dilute before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

EXP, if not refrigerated _____

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored at room temperature (up to 25°C) for a single period up to 6 months, but not exceeding the original expiry date.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/001 1 vial
EU/1/13/853/002 2 vials
EU/1/13/853/003 3 vials
EU/1/13/853/004 4 vials
EU/1/13/853/005 5 vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Remsima 100 mg

## 17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Remsima 100 mg powder for concentrate
infliximab
IV

## 2. METHOD OF ADMINISTRATION

For intravenous use after reconstitution and dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON FOR PRE-FILLED SYRINGE WITH AUTOMATIC NEEDLE GUARD**

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 120 mg solution for injection in pre-filled syringe
infliximab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL single dose pre-filled syringe contains 120 mg of infliximab.

## 3. LIST OF EXCIPIENTS

Excipients: acetic acid, sodium acetate trihydrate, sorbitol, polysorbate 80, water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe with 2 alcohol pads
1 pre-filled syringe with needle guard with 2 alcohol pads
2 pre-filled syringes with 2 alcohol pads
2 pre-filled syringes with needle guard with 2 alcohol pads
4 pre-filled syringes with 4 alcohol pads
4 pre-filled syringes with needle guard with 4 alcohol pads
6 pre-filled syringes with 6 alcohol pads
6 pre-filled syringes with needle guard with 6 alcohol pads

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CELLTRION Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/006 1 pre-filled syringe
EU/1/13/853/009 1 pre-filled syringe with automatic needle guard
EU/1/13/853/007 2 pre-filled syringes
EU/1/13/853/010 2 pre-filled syringes with automatic needle guard
EU/1/13/853/008 4 pre-filled syringes
EU/1/13/853/011 4 pre-filled syringes with automatic needle guard
EU/1/13/853/015 6 pre-filled syringes
EU/1/13/853/016 6 pre-filled syringes with automatic needle guard

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Remsima 120 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR PRE-FILLED SYRINGE WITH AUTOMATIC NEEDLE GUARD**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Remsima 120 mg injection
infliximab
SC

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mg

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON FOR PRE-FILLED PEN**

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 120 mg solution for injection in pre-filled pen
infliximab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 mL single dose pre-filled pen contains 120 mg of infliximab.

## 3. LIST OF EXCIPIENTS

Excipients: acetic acid, sodium acetate trihydrate, sorbitol, polysorbate 80, water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen with 2 alcohol pads
2 pre-filled pens with 2 alcohol pads
4 pre-filled pens with 4 alcohol pads
6 pre-filled pens with 6 alcohol pads

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. Keep the pre-filled pen in the outer carton in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CELLTRION Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/012 1 pre-filled pen
EU/1/13/853/013 2 pre-filled pens
EU/1/13/853/014 4 pre-filled pens
EU/1/13/853/017 6 pre-filled pens

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Remsima 120 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR PRE-FILLED PEN**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Remsima 120 mg injection
infliximab
Subcutaneous use

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mg

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 40 mg/mL concentrate for solution for infusion
infliximab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 100 mg of infliximab (40 mg/mL).

## 3. LIST OF EXCIPIENTS

Excipients: acetic acid, sodium acetate trihydrate, sorbitol, polysorbate 80, water for injections .

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

1 vial
2 vials
3 vials
4 vials
5 vials

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
See leaflet for further information

For intravenous use after dilution

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Patients with hereditary fructose intolerance (HFI) must not be given this medicine due to sorbitol content. See package leaflet for further information.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored at room temperature (up to 30°C) for a single period up to 15 days, but not exceeding the original expiry date.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/018 1 vial
EU/1/13/853/019 2 vials
EU/1/13/853/020 3 vials
EU/1/13/853/021 4 vials
EU/1/13/853/022 5 vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Remsima 40 mg/mL concentrate for solution for infusion
infliximab
IV

## 2. METHOD OF ADMINISTRATION

For intravenous use after dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg / mL
100 mg / 2.5 mL

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Remsima 40 mg/mL concentrate for solution for infusion
infliximab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 350 mg of infliximab (40 mg/mL).

## 3. LIST OF EXCIPIENTS

Excipients: acetic acid, sodium acetate trihydrate, sorbitol, polysorbate 80, water for injections

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.

1 vial
2 vials
3 vials
4 vials
5 vials

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
See leaflet for further information

For intravenous use after dilution

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

Patients with hereditary fructose intolerance (HFI) must not be given this medicine due to sorbitol content. See package leaflet for further information.

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored at room temperature (up to 30°C) for a single period up to 15 days, but not exceeding the original expiry date.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celltrion Healthcare Hungary Kft.
1062 Budapest
Váci út 1-3. WestEnd Office Building B torony
Hungary

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/853/023 1 vial
EU/1/13/853/024 2 vials
EU/1/13/853/025 3 vials
EU/1/13/853/026 4 vials
EU/1/13/853/027 5 vials

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE INDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE INDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Remsima 40 mg/mL concentrate for solution for infusion
infliximab
IV

## 2. METHOD OF ADMINISTRATION

For intravenous use after dilution

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg / mL
350 mg / 8.75 mL

## 6. OTHER

# Remsima

Infliximab

# Patient Reminder Card

Show this card to any doctor involved in your treatment.

This Patient Reminder Card contains important safety information that you need to be aware of before and during treatment with Remsima.

Name patient:
Name doctor:
Telephone number doctor:

When starting a new card, please keep this card as a reference for 4 months after your last dose of Remsima.

Please read the Remsima 'Package Leaflet' carefully before you start using this medicine.

Date of Remsima therapy initiation:

Current administrations:

It is important that you and your doctor record the brand name and batch number of your medicine.

Brand name:
Batch number:

Ask your doctor to record the type and date of last screening(s) for tuberculosis (TB) below:

| | |
|---|---|
| Test: | Test: |
| Date: | Date: |
| Result: | Result: |

Please make sure you also have a list of all other medicines that you are using with you at any visit to a healthcare professional.

List of allergies:

List of other medicines:

## Infections

**Before treatment with Remsima**

- Tell your doctor if you have an infection even if it is a very minor one.
- It is very important that you tell your doctor if you have ever had tuberculosis (TB), or if you have been in close contact with someone who has had TB. Your doctor will test you to see if you have TB. Ask your doctor to record the type and date of your last screening(s) for TB on the card.
- Tell your doctor if you have hepatitis B or if you know or suspect you are a carrier of the hepatitis B virus.

**During treatment with Remsima**

- Tell your doctor straight away if you have signs of an infection. Signs include a fever, feeling tired, (persistent) cough, shortness of breath, weight loss, night sweats, diarrhoea, wounds, dental problems, burning when urinating or 'flu-like' signs.

## Pregnancy, Breast-feeding and Vaccinations

- In case you have received Remsima while you were pregnant or if you are breast-feeding, it is important that you inform your baby's doctor about it before your baby receives any vaccine. Your baby should not receive a 'live vaccine', such as BCG (used to prevent tuberculosis) within 12 months after birth or while you are breast-feeding, unless your baby's doctor recommends otherwise.

## Hereditary Fructose Intolerance

- Remsima 100 mg and 350 mg concentrate for solution for infusion contains sorbitol. If you have hereditary fructose intolerance (HFI), you must not have that intravenously administered formulation.
- Tell your doctor if you have hereditary fructose intolerance. In that case, there are other suitable intravenous infliximab formulations available.

Keep this card with you for 4 months after your last dose of Remsima, or in case of pregnancy, for 12 months after the birth of your baby. Side effects may occur a long time after your last dose.

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Remsima 100 mg powder for concentrate for solution for infusion**
infliximab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a patient reminder card, which contains important safety information you need to be aware of before and during your treatment with Remsima.
- When starting a new card, keep this card as a reference for 4 months after your last dose of Remsima.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Remsima is and what it is used for

Remsima contains the active substance infliximab. Infliximab is a monoclonal antibody - a type of protein that attaches to a specific target in the body called TNF (tumour necrosis factor) alpha.

Remsima belongs to a group of medicines called 'TNF blockers'. It is used in adults for the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis (Bechterew's disease)
- Psoriasis.

Remsima is also used in adults and children 6 years of age or older for:
- Crohn's disease
- Ulcerative colitis.

Remsima works by selectively attaching to TNF alpha and blocking its action. TNF alpha is involved in inflammatory processes of the body so blocking it can reduce the inflammation in your body.

**Rheumatoid arthritis**
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima which you will take with another medicine called methotrexate to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Psoriatic arthritis**
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Ankylosing spondylitis (Bechterew's disease)**
Ankylosing spondylitis is an inflammatory disease of the spine. If you have ankylosing spondylitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- improve your physical function.

**Psoriasis**
Psoriasis is an inflammatory disease of the skin. If you have moderate to severe plaque psoriasis, you will first be given other medicines or treatments, such as phototherapy. If these medicines or treatments do not work well enough, you will be given Remsima to reduce the signs and symptoms of your disease.

**Ulcerative colitis**
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to treat your disease.

**Crohn's disease**
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- treat active Crohn's disease,
- reduce the number of abnormal openings (fistulae) between your bowel and your skin that have not been controlled by other medicines or surgery.

## 2. What you need to know before you use Remsima

**You must not be given Remsima if**
- you are allergic to infliximab or any of the other ingredients of this medicine (listed in section 6),
- you are allergic to proteins that come from mice,
- you have tuberculosis (TB) or another serious infection such as pneumonia or sepsis (serious bacterial infection of the blood),
- you have heart failure that is moderate or severe.

Do not use Remsima if any of the above applies to you. If you are not sure, talk to your doctor before you are given Remsima.

**Warnings and precautions**
Talk to your doctor before or during treatment with Remsima if you have:

<u>Had treatment with any medicine containing infliximab before</u>

- Tell your doctor if you have had treatment with medicines containing infliximab in the past and are now starting Remsima treatment again.
- If you have had a break in your treatment with infliximab of more than 16 weeks, there is a higher risk for allergic reactions when you start the treatment again.

Infections

- Tell your doctor before you are given Remsima if you have an infection even if it is a very minor one.
- Tell your doctor before you are given Remsima if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are common. These infections are caused by specific types of fungi that can affect the lungs or other parts of your body.
- You may get infections more easily when you are being treated with Remsima. If you are 65 years of age or older, you have a greater risk.
- These infections may be serious and include tuberculosis, infections caused by viruses, fungi, bacteria or other organisms in the environment and sepsis that may be life-threatening.

Tell your doctor straight away if you get signs of infection during treatment with Remsima. Signs include fever, cough, flu-like signs, feeling unwell, red or hot skin, wounds or dental problems. Your doctor may recommend temporarily stopping Remsima.

Tuberculosis (TB)

- It is very important that you tell your doctor if you have ever had TB or if you have been in close contact with someone who has had or has TB.
- Your doctor will test you to see if you have TB. Cases of TB have been reported in patients treated with infliximab, even in patients who have already been treated with medicines for TB. Your doctor will record these tests on your patient reminder card.
- If your doctor feels that you are at risk for TB, you may be treated with medicines for TB before you are given Remsima.

Tell your doctor straight away if you get signs of TB during treatment with Remsima. Signs include persistent cough, weight loss, feeling tired, fever, night sweats.

Hepatitis B virus

- Tell your doctor before you are given Remsima if you are a carrier of hepatitis B or have ever had it.
- Tell your doctor if you think you might be at risk of contracting hepatitis B.
- Your doctor should test you for hepatitis B virus.
- Treatment with TNF blockers such as Remsima may result in reactivation of hepatitis B virus in patients who carry this virus, which can be life-threatening in some cases.
- If you experience reactivation of hepatitis B, your doctor may need to stop your treatment and may give you medicines such as effective antiviral therapy with supportive treatment.

Heart problems

- Tell your doctor if you have any heart problems, such as mild heart failure.
- Your doctor will want to closely monitor your heart.

Tell your doctor straight away if you get new or worsening signs of heart failure during treatment with Remsima. Signs include shortness of breath or swelling of your feet.

Cancer and lymphoma

- Tell your doctor before you are given Remsima if you have or have ever had lymphoma (a type of blood cancer) or any other cancer.
- Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher risk of developing lymphoma.
- Children and adults taking Remsima may have an increased risk of developing lymphoma or another cancer.

- Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage boys or young men and most had either Crohn's disease or ulcerative colitis. This type of cancer has usually resulted in death. Almost all patients had also received medicines containing azathioprine or mercaptopurine in addition to TNF-blockers.
- Some patients treated with infliximab have developed certain kinds of skin cancer. If there are any changes in your skin or growths on the skin during or after therapy, tell your doctor.
- Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking Remsima including those over 60 years of age, your doctor may recommend regular screening for cervical cancer.

Lung disease or heavy smoking

- Tell your doctor before you are given Remsima if you have a lung disease called chronic obstructive pulmonary disease (COPD) or if you are a heavy smoker.
- Patients with COPD and patients who are heavy smokers may have a higher risk of developing cancer with Remsima treatment.

Nervous system disease

- Tell your doctor before you are given Remsima if you have or have ever had a problem that affects your nervous system. This includes multiple sclerosis, Guillain-Barré syndrome, if you have fits or have been diagnosed with 'optic neuritis'.

Tell your doctor straight away if you get symptoms of a nerve disease during treatment with Remsima. Signs include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.

Abnormal skin openings

- Tell your doctor if you have any abnormal skin openings (fistulae) before you are given Remsima.

Vaccinations

- Talk to your doctor if you recently have had or are due to have a vaccine.
- You should receive recommended vaccinations before starting Remsima treatment. You may receive some vaccines during treatment with Remsima but you should not receive live vaccines (vaccines that contain a living but weakened infectious agent) while using Remsima because they may cause infections.
- If you received Remsima while you were pregnant, your baby may also be at higher risk for getting an infection as a result of receiving a live vaccine during the first year of life. It is important that you tell your baby's doctors and other health care professionals about your Remsima use so they can decide when your baby should receive any vaccine, including live vaccines such as the BCG vaccine (used to prevent tuberculosis).
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. For more information see section on Pregnancy,breast-feeding and fertility.

Therapeutic infectious agents

- Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Operations or dental procedures

- Tell your doctor if you are going to have any operations or dental procedures.

- Tell your surgeon or dentist that you are having treatment with Remsima by showing them your patient reminder card.

Liver problems

- Some patients receiving infliximab have developed serious liver problems.
- Tell your doctor straight away if you get symptoms of liver problems during treatment with Remsima. Signs include yellowing of the skin and eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.

Low blood counts

- In some patients receiving infliximab, the body may not make enough of the blood cells that help fight infections or help stop bleeding.
- Tell your doctor straight away if you get symptoms of low blood counts during treatment with Remsima. Signs include persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.

Immune system disorder

- Some patients receiving infliximab have developed symptoms of an immune system disorder called lupus.
- Tell your doctor straight away if you develop symptoms of lupus during treatment with Remsima. Signs include joint pain or a rash on cheeks or arms that is sensitive to the sun.

**Children and adolescents**
The information above also applies to children and adolescents. In addition:

- Some children and teenage patients who have received TNF-blockers such as infliximab have developed cancers, including unusual types, which sometimes resulted in death.
- More children taking infliximab developed infections as compared to adults.
- Children should receive recommended vaccinations before starting Remsima treatment. Children may receive some vaccines during treatment with Remsima but should not receive live vaccines while using Remsima.

Remsima should only be used in children if they are being treated for Crohn's disease or ulcerative colitis. These children must be 6 years of age or older.

If you are not sure if any of the above applies to you, talk to your doctor before you are given Remsima.

**Other medicines and Remsima**
Patients who have inflammatory diseases already take medicines to treat their problem. These medicines may cause side effects. Your doctor will advise you what other medicines you must keep using while you are having Remsima.

Tell your doctor if you are using, have recently used or might use any other medicines, including any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis or medicines obtained without a prescription, such as vitamins and herbal medicines.

In particular, tell your doctor if you are using any of the following medicines:
- Medicines that affect your immune system.
- Kineret (which contains anakinra). Remsima and Kineret should not be used together.
- Orencia (which contains abatacept). Remsima and Orencia should not be used together.

While using Remsima you should not receive live vaccines. If you were using Remsima during pregnancy or if you are receiving Remsima while breast-feeding, tell your baby's doctor and other health care professionals caring for your baby about your Remsima use before the baby receives any vaccines.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Remsima.

**Pregnancy, breast-feeding and fertility**
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Remsima should only be used during pregnancy or while breast-feeding if your doctor feels it is necessary for you.
- You should avoid getting pregnant when you are being treated with Remsima and for 6 months after you stop being treated with it. Discuss the use of contraception during this time with your doctor.
- If you received Remsima during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. If you received Remsima while pregnant, giving BCG vaccine (used to prevent tuberculosis) to your baby within 12 months after birth may result in infection with serious complications, including death. Live vaccines such as the the BCG vaccine should not be given to your baby within 12 months after birth, unless your baby's doctor recommends otherwise. For more information see section on vaccination.
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's doctor recommends otherwise.
- Severely decreased numbers of white blood cells have been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately.

**Driving and using machines**
Remsima is not likely to affect your ability to drive or use tools or machines. If you feel tired, dizzy, or unwell after having Remsima, do not drive or use any tools or machines.

**Remsima contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
However, before Remsima is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

**Remsima contains polysorbate 80**
This medicine contains 0.5 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions. Tell your doctor if you have/your child has any known allergies.

## 3. How Remsima will be given

**Rheumatoid arthritis**
The usual dose is 3 mg for every kg of body weight.

**Psoriatic arthritis, ankylosing spondylitis (Bechterew's disease), psoriasis, ulcerative colitis and Crohn's disease**
The usual dose is 5 mg for every kg of body weight.

**How Remsima is given**
- Remsima will be given to you by your doctor or nurse.
- Your doctor or nurse will prepare the medicine for infusion.
- The medicine will be given as an infusion (drip) (over 2 hours) into one of your veins, usually in your arm. After the third treatment, your doctor may decide to give your dose of Remsima over 1 hour.
- You will be monitored while you are given Remsima and also for 1 to 2 hours afterwards.

**How much Remsima is given**
- The doctor will decide your dose and how often you will be given Remsima. This will depend on your disease, weight and how well you respond to Remsima.
- The table below shows how often you will usually have this medicine after your first dose.

| | |
|---|---|
| 2nd dose | 2 weeks after your 1st dose |
| 3rd dose | 6 weeks after your 1st dose |
| Further doses | Every 6 to 8 weeks depending on your disease |

**Use in children and adolescents**
In children (6 years of age or older) treated for Crohn's disease or ulcerative colitis, the recommended dose is the same as for adults.

**If you are given too much Remsima**
As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. There are no known side effects of having too much of Remsima.

**If you forget or miss your Remsima infusion**
If you forget or miss an appointment to receive Remsima, make another appointment as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However some patients may experience serious side effects and may require treatment. Side effects may also occur after your treatment with Remsima has stopped.

**Tell your doctor straight away if you notice any of the following:**
- **Signs of an allergic reaction** such as swelling of your face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions may be serious or life-threatening. An allergic reaction could happen within 2 hours of your injection or later. More signs of allergic side effects that may happen up to 12 days after your injection include pain in the muscles, fever, joint or jaw pain, sore throat or headache.
- **Signs of a heart problem** such as chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea (feeling sick), vomiting, fluttering or pounding in your chest, a fast or a slow heartbeat, and swelling of your feet.
- **Signs of infection (including TB)** such as fever, feeling tired, cough which may be persistent, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, collection of pus in the gut or around the anus (abscess), dental problems or burning sensation when urinating.
- **Possible signs of cancer** including but not limited to swelling of lymph nodes, weight loss, fever, unusual skin nodules, changes in moles or skin colouring, or unusual vaginal bleeding.

- **Signs of a lung problem** such as coughing, breathing difficulties or tightness in the chest.
- **Signs of a nervous system problem (including eye problems)** such as signs of a stroke (sudden numbness or weakness of your face, arm or leg, especially on one side of your body; sudden confusion, trouble speaking or understanding; trouble seeing in one or both eyes, trouble walking, dizziness, loss of balance or coordination or a severe headache), fits, tingling/numbness in any part of your body, or weakness in arms or legs, changes in eyesight such as double vision or other eye problems.
- **Signs of a liver problem** (including hepatitis B infection when you have had hepatitis B in the past) such as yellowing of the skin or eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.
- **Signs of an immune system disorder called lupus** such as joint pain or a rash on cheeks or arms that is sensitive to the sun (lupus) or cough, shortness of breath, fever or skin rash (sarcoidosis).
- **Signs of low blood counts** such as persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.
- **Signs of serious skin problems** such as reddish-target-like spots or circular patches often with central blisters on the trunk, large areas of peeling and shedding (exfoliating) skin, ulcers of mouth, throat, nose, genitals and eyes or small pus-filled bumps that can spread over the body. These skin reactions can be accompanied by fever.

Tell your doctor straight away if you notice any of the above.

The following side effects have been observed with Remsima:

**Very common:** may affect more than 1 in 10 people
- Stomach pain, feeling sick
- Viral infections such as herpes or flu
- Upper respiratory infections such as sinusitis
- Headache
- Side effect due to an infusion
- Pain.

**Common:** may affect up to 1 in 10 people
- Changes in how your liver works, increase in liver enzymes (shown in blood tests)
- Lung or chest infections such as bronchitis or pneumonia
- Difficult or painful breathing, chest pain
- Bleeding in the stomach or intestines, diarrhoea, indigestion, heartburn, constipation
- Nettle-type rash (hives), itchy rash or dry skin
- Balance problems or feeling dizzy
- Fever, increased sweating
- Circulation problems such as low or high blood pressure
- Bruising, hot flush or nosebleed, warm, red skin (flushing)
- Feeling tired or weak
- Bacterial infections such as blood poisoning, abscess or infection of the skin (cellulitis)
- Infection of the skin due to a fungus
- Blood problems such as anaemia or low white blood cell count
- Swollen lymph nodes
- Depression, problems sleeping
- Eye problems, including red eyes and infections
- Fast heart beat (tachycardia) or palpitations
- Pain in the joints, muscles or back
- Urinary tract infection
- Psoriasis, skin problems such as eczema and hair loss
- Reactions at the injection site such as pain, swelling, redness or itching
- Chills, a build-up of fluid under the skin causing swelling
- Feeling numb or having a tingling feeling.

**Uncommon:** may affect up to 1 in 100 people

- Shortage of blood supply, swelling of a vein
- Collection of blood outside the blood vessels (haematoma) or bruising
- Skin problems such as blistering, warts, abnormal skin colouration or pigmentation, or swollen lips, or thickening of the skin, or red, scaly, and flaky skin
- Severe allergic reactions (e.g. anaphylaxis), an immune system disorder called lupus, allergic reactions to foreign proteins
- Wounds taking longer to heal
- Swelling of the liver (hepatitis) or gall bladder, liver damage
- Feeling forgetful, irritable, confused, nervous
- Eye problems including blurred or reduced vision, puffy eyes or sties
- New or worsening heart failure, slow heart rate
- Fainting
- Convulsions, nerve problems
- A hole in the bowel or blockage of the intestine, stomach pain or cramps
- Swelling of your pancreas (pancreatitis)
- Fungal infections such as yeast infection, or fungal infection of the nails
- Lung problems (such as oedema)
- Fluid around the lungs (pleural effusion)
- Narrowed airway in the lungs, causing difficulty breathing
- Inflamed lining of the lung, causing sharp chest pains that feel worse with breathing (pleurisy)
- Tuberculosis
- Kidney infections
- Low platelet count, too many white blood cells
- Infections of the vagina
- Blood test result showing ‘antibodies’ against your own body.
- Changes in cholesterol and fat levels in the blood.
- Weight gain (for most patients, the weight gain was small).

**Rare:** may affect up to 1 in 1,000 people

- A type of blood cancer (lymphoma)
- Your blood not supplying enough oxygen to your body, circulation problems such as narrowing of a blood vessel
- Inflammation of the lining of the brain (meningitis)
- Infections due to a weakened immune system
- Hepatitis B infection when you have had hepatitis B in the past
- Inflamed liver caused by a problem with the immune system (autoimmune hepatitis)
- Liver problem that causes yellowing of the skin or eyes (jaundice)
- Abnormal tissue swelling or growth
- Severe allergic reaction that may cause loss of consciousness and could be life-threatening (anaphylactic shock)
- Swelling of small blood vessels (vasculitis)
- Immune disorders that could affect the lungs, skin and lymph nodes (such as sarcoidosis)
- Collections of immune cells resulting from an inflammatory response (granulomatous lesions)
- Lack of interest or emotion
- Serious skin problems such as toxic epidermal necrolysis, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis
- Other skin problems such as erythema multiforme, blisters and peeling skin, or boils (furunculosis)
- Serious nervous system disorders such as transverse myelitis, multiple sclerosis-like disease, optic neuritis and Guillain-Barré syndrome
- Inflammation in the eye that may cause changes in the vision, including blindness
- Fluid in the lining of the heart (pericardial effusion)
- Serious lung problems (such as interstitial lung disease)

- Melanoma (a type of skin cancer)
- Cervical cancer
- Low blood counts, including a severely decreased number of white blood cells
- Small red or purple spots caused by bleeding under the skin
- Abnormal values of a blood protein called 'complement factor' which is part of the immune system
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes).

**Not known:** frequency cannot be estimated from the available data
- Cancer in children and adults
- A rare blood cancer affecting mostly teenage boys or young men (hepatosplenic T-cell lymphoma)
- Liver failure
- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Heart attack
- Stroke
- Temporary loss of sight during or within 2 hours of infusion
- Infection due to a live vaccine because of a weakened immune system.

**Additional side effects in children and adolescents**
Children who took infliximab for Crohn's disease showed some differences in side effects compared with adults who took infliximab for Crohn's disease. The side effects that happened more in children were: low red blood cells (anaemia), blood in stool, low overall levels of white blood cells (leukopenia), redness or blushing (flushing), viral infections, low levels of white blood cells that fight infection (neutropenia), bone fracture, bacterial infection and allergic reactions of the breathing tract.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Remsima

Remsima will generally be stored by the health professionals. The storage details should you need them are as follows:
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C).
- This medicine can also be stored in the original carton outside of refrigerated storage up to a maximum of 25°C for a single period of up to six months, but not beyond the original expiry date. In this situation, do not return to refrigerated storage again. Write the new expiry date on the carton including day/month/year. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- It is recommended that when Remsima is prepared for infusion, it is used as soon as possible (within 3 hours). However, if the solution is prepared in germ-free conditions, it can be stored in a refrigerator at 2°C – 8°C up to 60 days and for an additional 24 hours at 25 °C after removal from the refrigerator.
- Do not use this medicine if it is discoloured or if there are particles present.

## 6. Contents of the pack and other information

**What Remsima contains**
- The active substance is infliximab. Each vial contains 100 mg of infliximab. After preparation each mL contains 10 mg of infliximab.
- The other ingredients are sucrose, polysorbate 80 (E433), sodium dihydrogen phosphate monohydrate and disodium phosphate dihydrate.

**What Remsima looks like and contents of the pack**
Remsima is supplied as a glass vial containing a powder for concentrate for solution for infusion. The powder is white.

Remsima is produced in packs of 1, 2, 3, 4 or 5 vials. Not all pack sizes may be marketed.

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**This leaflet was last revised in {MM/YYYY}.**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:

Patients treated with Remsima should be given the patient reminder card.

**Instructions for use and handling – storage conditions**

Store at 2°C – 8°C.

Remsima may be stored at temperatures up to a maximum of 25°C for a single period of up to 6 months, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Remsima must not be returned to refrigerated storage.

**Instructions for use and handling – reconstitution, dilution and administration**

In order to improve the traceability of biological medicinal products, the name and batch number of the administered medicinal product should be clearly recorded.

1. The dose and the number of Remsima vials have to be calculated. Each Remsima vial contains 100 mg infliximab. The required total volume of reconstituted Remsima solution has to be calculated.

2. Under aseptic conditions, each Remsima vial should be reconstituted with 10 mL of water for injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. The flip-top from the vial has to be removed and the top has to be wiped with a 70% alcohol swab. The syringe needle should be inserted into the vial through the centre of the rubber stopper and the stream of water for injections directed to the glass wall of the vial. The solution has to be gently swirled by rotating the vial to dissolve the powder. Prolonged or vigorous agitation must be avoided. THE VIAL MUST NOT BE SHAKEN. Foaming of the solution on reconstitution may occur. The reconstituted solution should stand for 5 minutes. The solution should be colourless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. The solution must not be used if opaque particles, discolouration, or other foreign particles are present.

3. The required volume of the reconstituted Remsima solution should be diluted to 250 mL with sodium chloride 9 mg/mL (0.9%) solution for infusion. Do not dilute the reconstituted Remsima solution with any other diluent. The dilution can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250-mL glass bottle or infusion bag equal to the volume of reconstituted Remsima. The required volume of reconstituted Remsima solution should slowly be added to the 250-mL infusion bottle or bag and gently be mixed. For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL, 1000 mL) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/ mL. If stored refrigerated after reconstitution and dilution, the infusion solution must be allowed to equilibrate at room temperature to 25 °C for 3 hours prior to Step 4 (infusion). Storage beyond 24 hours at 2 °C - 8 °C applies to preparation of Remsima in the infusion bag only.

4. The infusion solution has to be administered over a period of not less than the infusion time recommended (see section 3). Only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometre or less) should be used. Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of reconstitution and dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has been taken place in controlled and validated aseptic conditions. Any unused portion of the infusion solution should not be stored for reuse.

5. Remsima should be visually inspected for particulate matter or discolouration prior to administration. If visibly opaque particles, discolouration or foreign particles are observed it should not be used.

6. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**Package leaflet: Information for the user**

**Remsima 120 mg solution for injection in pre-filled syringe**
infliximab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a patient reminder card, which contains important safety information you need to be aware of before and during your treatment with Remsima.
- When starting a new card, keep this card as a reference for 4 months after your last dose of Remsima.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Remsima is and what it is used for

Remsima contains the active substance infliximab. Infliximab is a monoclonal antibody - a type of protein that attaches to a specific target in the body called TNF (tumour necrosis factor) alpha.

Remsima belongs to a group of medicines called 'TNF blockers'. It is used in adults for the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis (Bechterew's disease)
- Psoriasis
- Crohn's disease
- Ulcerative colitis.

Remsima works by selectively attaching to TNF alpha and blocking its action. TNF alpha is involved in inflammatory processes of the body so blocking it can reduce the inflammation in your body.

**Rheumatoid arthritis**
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima which you will take with another medicine called methotrexate to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Psoriatic arthritis**
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Ankylosing spondylitis (Bechterew's disease)**
Ankylosing spondylitis is an inflammatory disease of the spine. If you have ankylosing spondylitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- improve your physical function.

**Psoriasis**
Psoriasis is an inflammatory disease of the skin. If you have moderate to severe plaque psoriasis, you will first be given other medicines or treatments, such as phototherapy. If these medicines or treatments do not work well enough, you will be given Remsima to reduce the signs and symptoms of your disease.

**Ulcerative colitis**
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to treat your disease.

**Crohn's disease**
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- treat active Crohn's disease,
- reduce the number of abnormal openings (fistulae) between your bowel and your skin that have not been controlled by other medicines or surgery.

## 2. What you need to know before you use Remsima

**You must not use Remsima if**
- you are allergic to infliximab or any of the other ingredients of this medicine (listed in section 6),
- you are allergic to proteins that come from mice,
- you have tuberculosis (TB) or another serious infection such as pneumonia or sepsis (serious bacterial infection of the blood),
- you have heart failure that is moderate or severe.

Do not use Remsima if any of the above applies to you. If you are not sure, talk to your doctor before you are given Remsima.

**Warnings and precautions**
Talk to your doctor before or during treatment with Remsima if you have:

<u>Had treatment with any medicine containing infliximab before</u>

- Tell your doctor if you have had treatment with medicines containing infliximab in the past and are now starting Remsima treatment again.
- If you have had a break in your treatment with infliximab of more than 16 weeks, there is a higher risk for allergic reactions when you start the treatment again.

Local injection site reactions

- Some patients receiving infliximab via injection under the skin have experienced local injection site reactions. Signs of a local injection site reaction can include redness, pain, itching, swelling, hardness, bruising, bleeding, cold sensation, tingling sensation, irritation, rash, ulcer, hives, blisters and scab on the skin of the injection site.
- Most of these reactions are mild to moderate and mostly resolve on their own within a day.

Infections

- Tell your doctor before you are given Remsima if you have an infection even if it is a very minor one.
- Tell your doctor before you are given Remsima if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are common. These infections are caused by specific types of fungi that can affect the lungs or other parts of your body.
- You may get infections more easily when you are being treated with Remsima. If you are 65 years of age or older, you have a greater risk.
- These infections may be serious and include tuberculosis, infections caused by viruses, fungi, bacteria or other organisms in the environment and sepsis that may be life-threatening.

Tell your doctor straight away if you get signs of infection during treatment with Remsima. Signs include fever, cough, flu-like signs, feeling unwell, red or hot skin, wounds or dental problems. Your doctor may recommend temporarily stopping Remsima.

Tuberculosis (TB)

- It is very important that you tell your doctor if you have ever had TB or if you have been in close contact with someone who has had or has TB.
- Your doctor will test you to see if you have TB. Cases of TB have been reported in patients treated with infliximab, even in patients who have already been treated with medicines for TB. Your doctor will record these tests on your patient reminder card.
- If your doctor feels that you are at risk for TB, you may be treated with medicines for TB before you are given Remsima.

Tell your doctor straight away if you get signs of TB during treatment with Remsima. Signs include persistent cough, weight loss, feeling tired, fever, night sweats.

Hepatitis B virus

- Tell your doctor before you are using Remsima if you are a carrier of hepatitis B or have ever had it.
- Tell your doctor if you think you might be at risk of contracting hepatitis B.
- Your doctor should test you for hepatitis B virus.
- Treatment with TNF blockers such as Remsima may result in reactivation of hepatitis B virus in patients who carry this virus, which can be life-threatening in some cases.
- If you experience reactivation of hepatitis B, your doctor may need to stop your treatment and may give you medicines such as effective antiviral therapy with supportive treatment.

Heart problems

- Tell your doctor if you have any heart problems, such as mild heart failure.
- Your doctor will want to closely monitor your heart.

Tell your doctor straight away if you get new or worsening signs of heart failure during treatment with Remsima. Signs include shortness of breath or swelling of your feet.

Cancer and lymphoma

- Tell your doctor before you are given Remsima if you have or have ever had lymphoma (a type of blood cancer) or any other cancer.
- Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher risk of developing lymphoma.
- Patients taking Remsima may have an increased risk of developing lymphoma or another cancer.
- Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage boys or young men and most had either Crohn's disease or ulcerative colitis. This type of cancer has usually resulted in death. Almost all patients had also received medicines containing azathioprine or mercaptopurine in addition to TNF-blockers.
- Some patients treated with infliximab have developed certain kinds of skin cancer. If there are any changes in your skin or growths on the skin during or after therapy, tell your doctor.
- Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking Remsima including those over 60 years of age, your doctor may recommend regular screening for cervical cancer.

Lung disease or heavy smoking

- Tell your doctor before you are given Remsima if you have a lung disease called chronic obstructive pulmonary disease (COPD) or if you are a heavy smoker.
- Patients with COPD and patients who are heavy smokers may have a higher risk of developing cancer with Remsima treatment.

Nervous system disease

- Tell your doctor before you are given Remsima if you have or have ever had a problem that affects your nervous system. This includes multiple sclerosis, Guillain-Barré syndrome, if you have fits or have been diagnosed with 'optic neuritis'.

Tell your doctor straight away if you get symptoms of a nerve disease during treatment with Remsima. Signs include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.

Abnormal skin openings

- Tell your doctor if you have any abnormal skin openings (fistulae) before you are given Remsima.

Vaccinations

- Talk to your doctor if you recently have had or are due to have a vaccine.
- You should receive recommended vaccinations before starting Remsima treatment. You may receive some vaccines during treatment with Remsima but you should not receive live vaccines (vaccines that contain a living but weakened infectious agent) while using Remsima because they may cause infections.
- If you received Remsima while you were pregnant, your baby may also be at higher risk for getting an infection as a result of receiving a live vaccine during the first year of life. It is important that you tell your baby's doctors and other health care professionals about your Remsima use so they can decide when your baby should receive any vaccine, including live vaccines such as the BCG vaccine (used to prevent tuberculosis).
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. For more information see section on Pregnancy, breast-feeding and fertility.

Therapeutic infectious agents

- Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Operations or dental procedures

- Tell your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist that you are having treatment with Remsima by showing them your patient reminder card.

Liver problems

- Some patients receiving infliximab have developed serious liver problems.
- Tell your doctor straight away if you get symptoms of liver problems during treatment with Remsima. Signs include yellowing of the skin and eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.

Low blood counts

- In some patients receiving infliximab, the body may not make enough of the blood cells that help fight infections or help stop bleeding.
- Tell your doctor straight away if you get symptoms of low blood counts during treatment with Remsima. Signs include persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.

Immune system disorder

- Some patients receiving infliximab have developed symptoms of an immune system disorder called lupus.
- Tell your doctor straight away if you develop symptoms of lupus during treatment with Remsima. Signs include joint pain or a rash on cheeks or arms that is sensitive to the sun.

**Children and adolescents**
Do not give this medicine to children and adolescents under 18 years of age because there are no data that show that this medicine is safe and works in this age group.

**Other medicines and Remsima**
Patients who have inflammatory diseases already take medicines to treat their problem. These medicines may cause side effects. Your doctor will advise you what other medicines you must keep using while you are having Remsima.

Tell your doctor if you are using, have recently used or might use any other medicines, including any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis or medicines obtained without a prescription, such as vitamins and herbal medicines.

In particular, tell your doctor if you are using any of the following medicines:
- Medicines that affect your immune system.
- Kineret (which contains anakinra). Remsima and Kineret should not be used together.
- Orencia (which contains abatacept). Remsima and Orencia should not be used together.

While using Remsima you should not receive live vaccines. If you were using Remsima during pregnancy or if you are receiving Remsima while breast-feeding, tell your baby's doctor and other health care professionals caring for your baby about your Remsima use before the baby receives any vaccines.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Remsima.

**Pregnancy, breast-feeding and fertility**
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Remsima should only be used during pregnancy or while breast-feeding if your doctor feels it is necessary for you.
- You should avoid getting pregnant when you are being treated with Remsima and for 6 months after you stop being treated with it. Discuss the use of contraception during this time with your doctor.
- If you received Remsima during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. If you received Remsima while pregnant, giving BCG vaccine (used to prevent tuberculosis) to your baby within 12 months after birth may result in infection with serious complications, including death. Live vaccines such as the BCG vaccine should not be given to your baby within 12 months after birth, unless your baby's doctor recommends otherwise. For more information see section on vaccination.
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's doctor recommends otherwise.
- Severely decreased numbers of white blood cells have been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately.

**Driving and using machines**
Remsima is not likely to affect your ability to drive or use tools or machines. If you feel tired, dizzy, or unwell after having Remsima, do not drive or use any tools or machines.

**Remsima contains sodium and sorbitol**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free' and 45 mg sorbitol in each 120 mg dose.

**Remsima contains polysorbate 80**
This medicine contains 0.5 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

## 3. How to use Remsima

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

**Rheumatoid arthritis**
Your doctor will start your treatment with or without two infliximab intravenous infusion doses of 3 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). If infliximab intravenous infusion doses are given to start the treatment, they are administered 2 weeks apart via intravenous infusion. After 4 weeks from the last intravenous infusion, you will be given Remsima via injection under the skin (subcutaneous injection). If Remsima subcutaneous injection doses are given to start the treatment, Remsima 120 mg should be given as a subcutaneous injection followed by additional subcutaneous injections at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter.
The usual recommended dose of Remsima subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**Psoriatic arthritis, ankylosing spondylitis (Bechterew's disease) and psoriasis**

Your doctor will start your treatment with two infliximab intravenous infusion doses of 5 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). They are administered 2 weeks apart via intravenous infusion. After 4 weeks from the last intravenous infusion, you will be given Remsima via injection under the skin (subcutaneous injection).
The usual recommended dose of Remsima subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**Crohn's disease and ulcerative colitis**
Your doctor will start your treatment with two or three infliximab intravenous infusion doses of 5 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). They are administered 2 weeks apart via intravenous infusion and additional intravenous infusion may be given 4 weeks after the second infusion. After 4 weeks from the last intravenous infusion, you will be given Remsima via injection under the skin (subcutaneous injection).
The usual recommended dose of Remsima subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**How Remsima is given**
- Remsima 120 mg solution for injection is administered by injection under the skin (subcutaneous use) only. It is important to check the product labels to ensure that the correct formulation is being given as prescribed.
- For patients with rheumatoid arthritis, your doctor may start your Remsima treatment with or without infliximab intravenous infusion doses. For patients with ankylosing spondylitis, psoriatic arthritis or psoriasis, two infliximab intravenous infusion doses will be given to start your Remsima treatment. For patients with Crohn's disease or ulcerative colitis, two or three infliximab intravenous infusion doses will be given to start your Remsima treatment.
- For rheumatoid arthritis patients, if Remsima treatment is initiated without two infliximab intravenous infusion doses, the table below shows how often you will usually have Remsima 120 mg subcutaneous after your first dose.

| | |
|---|---|
| 2nd dose | 1 week after your 1st dose |
| 3rd dose | 2 weeks after your 1st dose |
| 4th dose | 3 weeks after your 1st dose |
| 5th dose | 4 weeks after your 1st dose |
| Further doses | 6 weeks after your 1st dose and every 2 weeks thereafter |

- Infliximab intravenous infusion doses will be given 2 weeks apart by your doctor or nurse and additional intravenous infusion may be given 4 weeks after the second infusion for Crohn's disease and ulcerative colitis patients under your doctor's discretion to start your Remsima treatment. The first Remsima subcutaneous injection will be given 4 weeks after the last intravenous infusion followed by Remsima subcutaneous injections given every 2 weeks.
- The first subcutaneous injection of Remsima will be administered under the supervision of your doctor.
- After proper training, if you feel you are well-trained and confident to inject Remsima yourself, your doctor may allow you to inject subsequent doses of Remsima yourself at home.
- Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed **"Instructions for Use"** at the end of this leaflet.

**If you use more Remsima than you should**
If you have used more Remsima than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor, pharmacist or nurse immediately. Always have the outer carton of the medicine with you, even if it is empty.

**If you forget to use Remsima**

Missed dose for up to 7 days

If you miss a dose of Remsima for up to 7 days, after the original scheduled dose, you should take the missed dose immediately. Take your next dose on the next originally planned date and then follow the original dosing schedule.

Missed dose for 8 days or more
If you miss a dose of Remsima for 8 days or more, after the original scheduled dose, you should not take the missed dose. Take your next dose on the next originally planned date and then follow the original dosing schedule.

If you are not sure when to inject Remsima, call your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However some patients may experience serious side effects and may require treatment. Side effects may also occur after your treatment with Remsima has stopped.

**Tell your doctor straight away if you notice any of the following:**
- **Signs of an allergic reaction** such as swelling of your face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions may be serious or life-threatening. An allergic reaction could happen within 2 hours of your injection or later. More signs of allergic side effects that may happen up to 12 days after your injection include pain in the muscles, fever, joint or jaw pain, sore throat or headache.
- **Signs of a local injection site reaction** such as redness, pain, itching, swelling, hardness, bruising, bleeding, cold sensation, tingling sensation, irritation, rash, ulcer, hives, blisters and scab.
- **Signs of a heart problem** such as chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea (feeling sick), vomiting, fluttering or pounding in your chest, a fast or a slow heartbeat, and swelling of your feet.
- **Signs of infection (including TB)** such as fever, feeling tired, cough which may be persistent, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, collection of pus in the gut or around the anus (abscess), dental problems or burning sensation when urinating.
- **Possible signs of cancer** including but not limited to swelling of lymph nodes, weight loss, fever, unusual skin nodules, changes in moles or skin colouring, or unusual vaginal bleeding.
- **Signs of a lung problem** such as coughing, breathing difficulties or tightness in the chest.
- **Signs of a nervous system problem (including eye problems)** such as signs of a stroke (sudden numbness or weakness of your face, arm or leg, especially on one side of your body; sudden confusion, trouble speaking or understanding; trouble seeing in one or both eyes, trouble walking, dizziness, loss of balance or coordination or a severe headache), fits, tingling/numbness in any part of your body, or weakness in arms or legs, changes in eyesight such as double vision or other eye problems.
- **Signs of a liver problem** (including hepatitis B infection when you have had hepatitis B in the past) such as yellowing of the skin or eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.
- **Signs of an immune system disorder called lupus** such as joint pain or a rash on cheeks or arms that is sensitive to the sun (lupus) or cough, shortness of breath, fever or skin rash (sarcoidosis).
- **Signs of low blood counts** such as persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.

- **Signs of serious skin problems** such as reddish-target-like spots or circular patches often with central blisters on the trunk, large areas of peeling and shedding (exfoliating) skin, ulcers of mouth, throat, nose, genitals and eyes or small pus-filled bumps that can spread over the body. These skin reactions can be accompanied by fever.

Tell your doctor straight away if you notice any of the above.

The following side effects have been observed with Remsima:

**Very common:** may affect more than 1 in 10 people
- Stomach pain, feeling sick
- Viral infections such as herpes or flu
- Upper respiratory infections such as sinusitis
- Headache
- Side effect due to an injection
- Pain.

**Common:** may affect up to 1 in 10 people
- Changes in how your liver works, increase in liver enzymes (shown in blood tests)
- Lung or chest infections such as bronchitis or pneumonia
- Difficult or painful breathing, chest pain
- Bleeding in the stomach or intestines, diarrhoea, indigestion, heartburn, constipation
- Nettle-type rash (hives), itchy rash or dry skin
- Balance problems or feeling dizzy
- Fever, increased sweating
- Circulation problems such as low or high blood pressure
- Bruising, hot flush or nosebleed, warm, red skin (flushing)
- Feeling tired or weak
- Bacterial infections such as blood poisoning, abscess or infection of the skin (cellulitis)
- Infection of the skin due to a fungus
- Blood problems such as anaemia or low white blood cell count
- Swollen lymph nodes
- Depression, problems sleeping
- Eye problems, including red eyes and infections
- Fast heart beat (tachycardia) or palpitations
- Pain in the joints, muscles or back
- Urinary tract infection
- Psoriasis, skin problems such as eczema and hair loss
- Reactions at the injection site such as pain, swelling, redness or itching
- Chills, a build-up of fluid under the skin causing swelling
- Feeling numb or having a tingling feeling.

**Uncommon:** may affect up to 1 in 100 people
- Shortage of blood supply, swelling of a vein
- Collection of blood outside the blood vessels (haematoma) or bruising
- Skin problems such as blistering, warts, abnormal skin colouration or pigmentation, or swollen lips, or thickening of the skin, or red, scaly, and flaky skin
- Severe allergic reactions (e.g. anaphylaxis), an immune system disorder called lupus, allergic reactions to foreign proteins
- Wounds taking longer to heal
- Swelling of the liver (hepatitis) or gall bladder, liver damage
- Feeling forgetful, irritable, confused, nervous
- Eye problems including blurred or reduced vision, puffy eyes or sties
- New or worsening heart failure, slow heart rate
- Fainting

- Convulsions, nerve problems
- A hole in the bowel or blockage of the intestine, stomach pain or cramps
- Swelling of your pancreas (pancreatitis)
- Fungal infections such as yeast infection, or fungal infection of the nails
- Lung problems (such as oedema)
- Fluid around the lungs (pleural effusion)
- Narrowed airway in the lungs, causing difficulty breathing
- Inflamed lining of the lung, causing sharp chest pains that feel worse with breathing (pleurisy)
- Tuberculosis
- Kidney infections
- Low platelet count, too many white blood cells
- Infections of the vagina
- Blood test result showing 'antibodies' against your own body
- Changes in cholesterol and fat levels in the blood.
- Weight gain (for most patients, the weight gain was small).

**Rare:** may affect up to 1 in 1,000 people
- A type of blood cancer (lymphoma)
- Your blood not supplying enough oxygen to your body, circulation problems such as narrowing of a blood vessel
- Inflammation of the lining of the brain (meningitis)
- Infections due to a weakened immune system
- Hepatitis B infection when you have had hepatitis B in the past
- Inflamed liver caused by a problem with the immune system (autoimmune hepatitis)
- Liver problem that causes yellowing of the skin or eyes (jaundice)
- Abnormal tissue swelling or growth
- Severe allergic reaction that may cause loss of consciousness and could be life-threatening (anaphylactic shock)
- Swelling of small blood vessels (vasculitis)
- Immune disorders that could affect the lungs, skin and lymph nodes (such as sarcoidosis)
- Collections of immune cells resulting from an inflammatory response (granulomatous lesions)
- Lack of interest or emotion
- Serious skin problems such as toxic epidermal necrolysis, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis
- Other skin problems such as erythema multiforme, blisters and peeling skin, or boils (furunculosis)
- Serious nervous system disorders such as transverse myelitis, multiple sclerosis-like disease, optic neuritis and Guillain-Barré syndrome
- Inflammation in the eye that may cause changes in the vision, including blindness
- Fluid in the lining of the heart (pericardial effusion)
- Serious lung problems (such as interstitial lung disease)
- Melanoma (a type of skin cancer)
- Cervical cancer
- Low blood counts, including a severely decreased number of white blood cells
- Small red or purple spots caused by bleeding under the skin
- Abnormal values of a blood protein called 'complement factor' which is part of the immune system
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes).

**Not known:** frequency cannot be estimated from the available data
- Cancer
- A rare blood cancer affecting mostly young men (hepatosplenic T-cell lymphoma)
- Liver failure
- Merkel cell carcinoma (a type of skin cancer)

- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Heart attack
- Stroke
- Temporary loss of sight during or within 2 hours of infusion
- Infection due to a live vaccine because of a weakened immune system.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Remsima

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light.
- This medicine can also be stored in the original carton outside of refrigerated storage up to a maximum of 25°C for a single period of up to 28 days, but not beyond the original expiry date. In this situation, do not return to refrigerated storage again. Write the new expiry date on the carton including day/month/year. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Remsima contains**
- The active substance is infliximab. Each 1 ml single dose pre-filled syringe contains 120 mg of infliximab.
- The other ingredients are acetic acid, sodium acetate trihydrate, sorbitol (E420), polysorbate 80 (E433) and water for injections.

**What Remsima looks like and contents of the pack**
Remsima is a clear to opalescent, colourless to pale brown solution which is supplied as a single use pre-filled syringe.

Each pack contains 1 pre-filled syringe with 2 alcohol pads, 2 pre-filled syringes with 2 alcohol pads, 4 pre-filled syringes with 4 alcohol pads or 6 pre-filled syringes with 6 alcohol pads.

Each pack contains 1 pre-filled syringe with automatic needle guard with 2 alcohol pads, 2 pre-filled syringes with automatic needle guard with 2 alcohol pads, 4 pre-filled syringes with automatic needle guard with 4 alcohol pads or 6 pre-filled syringes with automatic needle guard with 6 alcohol pads.

Not all pack sizes may be marketed.

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**This leaflet was last revised in {MM/YYYY}.**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

## 7. Instructions for use

Read carefully these instructions before using the Remsima syringe. Consult your healthcare provider if you have questions about using the Remsima syringe.

**Important information**

- Use the syringe **ONLY if** your healthcare provider has trained you on the right way to prepare for and to give an injection.
- Ask your healthcare provider how often you will need to give an injection.
- Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.
- **Do not** use the syringe if it has been dropped or is visibly damaged. A damaged syringe may not function properly.
- **Do not** reuse the syringe.
- **Do not** shake the syringe at any time.

**About the Remsima syringe**

**Parts of the syringe (see *Figure A*):**

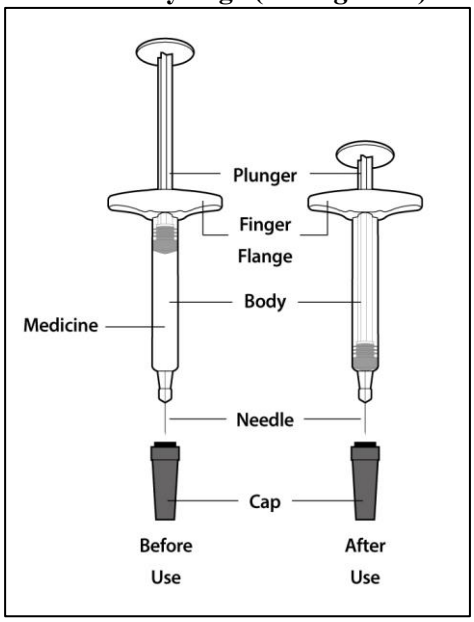


*Figure A*

- **Do not** remove the cap until you are ready to inject. Once you remove the cap, **do not** recap the syringe.

**Prepare for the injection**

**1. Gather the supplies for the injection.**

a. Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.
b. Remove the syringe from the carton stored in your refrigerator by holding the middle of the syringe body.
c. Ensure you have the following supplies:
   - Syringe
   - Alcohol swab
   - Cotton ball or gauze*
   - Adhesive bandage*
   - Sharps disposal container*

   **Items not included in the carton.*

**2. Inspect the syringe.**
**Do not** use the syringe if:

- It is cracked or damaged.
- The expiration date has passed.

**3. Inspect the medicine (see *Figure B*).**
The liquid should be clear and colourless to pale brown.
**Do not** use the syringe if the liquid is cloudy, discoloured or contains particles in it.
*Note: You may see air bubbles in the liquid. This is normal.*

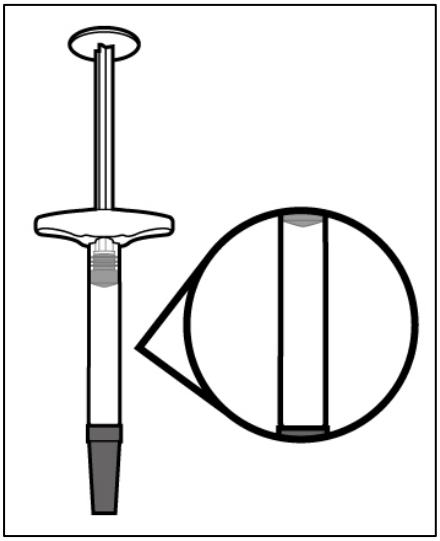

*Figure B*

**4. Wait 30 minutes.**

a. Leave the syringe at room temperature for 30 minutes to allow it to naturally warm up.

**Do not** warm the syringe using heat sources such as hot water or a microwave.

**5. Choose an injection site (see *Figure C*).**

a. Select an injection site. You may inject into:
   - The front of the thighs.
   - The abdomen except for the 5 cm around the belly button (navel).
   - The outer area of the upper arms (caregiver ONLY).

**Do not** inject into skin that is within 5 cm of your belly button (navel), or is tender, damaged, bruised, or scarred.
*Note: Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.*

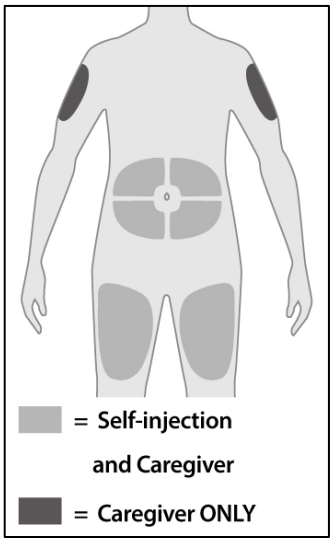


*Figure C*

**6. Wash your hands.**

a. Wash your hands with soap and water and dry them thoroughly.

**7. Clean the injection site.**

a. Clean the injection site with an alcohol swab.
b. Let the skin dry before injecting.

**Do not** blow on or touch the injection site again before giving the injection.

**Give the injection**

**8. Remove the cap (see *Figure D*).**

a. Pull the cap straight off and set it aside.

**Do not** touch the needle. Doing so may result in a needle stick injury.

*Note: It is normal to see a few drops of liquid come out of the needle upon the cap removal.*

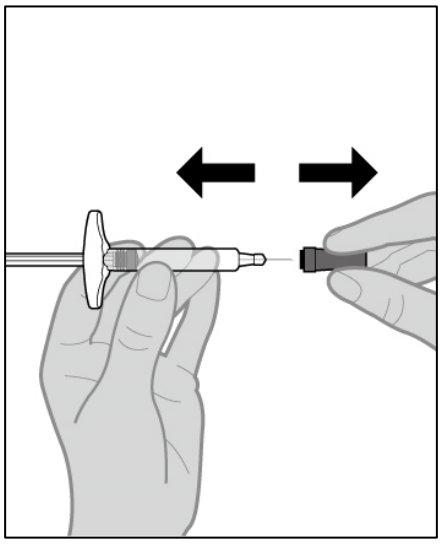

*Figure D*

**9. Insert the syringe into the injection site (see *Figure E*).**

a. Hold the syringe by its body in one hand between your thumb and index finger.
b. Using your other hand, gently pinch a fold of skin you cleaned.
c. With a quick and "dart-like" motion, insert the needle completely into the fold of the skin at a 45-degree angle.

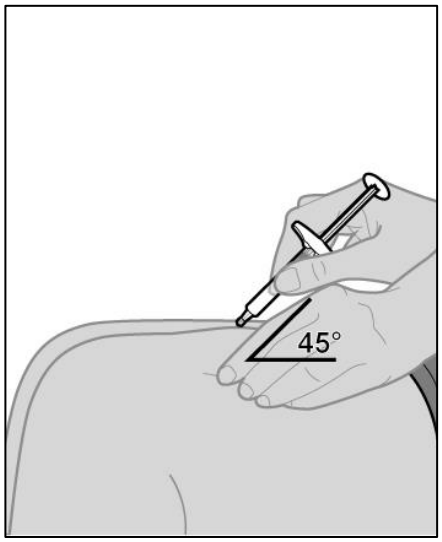


*Figure E*

**10. Give the injection (see *Figure F*).**

a. After the needle is inserted, let go of the pinched skin.
b. Push the plunger down slowly and as far as it will go until the syringe is empty.

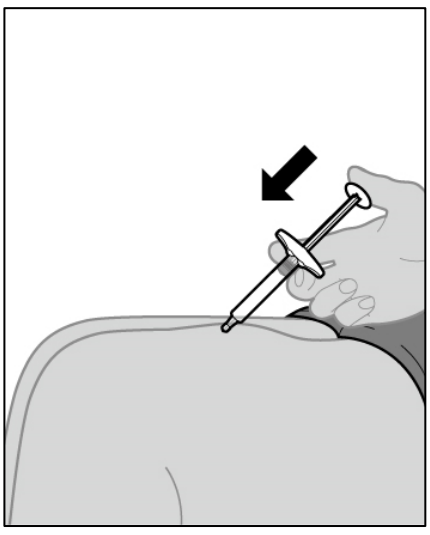

*Figure F*

**11. Remove the needle from the injection site (see *Figure G*).**

a. Remove the needle from the skin at the same angle it was inserted.
b. Gently press a cotton ball or gauze over the injection site and hold for 10 seconds.
c. Apply an adhesive bandage, if necessary.

**Do not** rub the injection site.

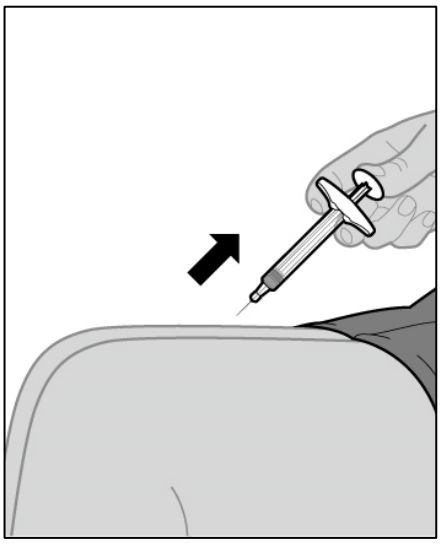

*Figure G*

**After the injection**

**12. Dispose of the syringe (see *Figure H*).**

a. Put the used syringe in an approved sharps disposal container immediately after use.
b. If you do not have an approved sharps disposal container, you may use a household container that is:
   - made of a heavy-duty plastic;
   - able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
   - upright and stable during use;
   - leak-resistant; and
   - properly labelled to warn of hazardous waste inside the container.
c. When your sharps disposal container is almost full, it should be disposed of in accordance with local requirements.

**Do not** recap the syringe.

*Note: Keep the syringe and sharps disposal container out of the sight and reach of children.*

*Figure H*

Read carefully these instructions before using the Remsima syringe. Consult your healthcare provider if you have questions about using the Remsima syringe.

**Important information**

- Use the syringe **ONLY if** your healthcare provider has trained you on the right way to prepare for and to give an injection.
- Ask your healthcare provider how often you will need to give an injection.
- Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.
- **Do not** use the syringe if it has been dropped or is visibly damaged. A damaged syringe may not function properly.
- **Do not** reuse the syringe.
- **Do not** shake the syringe at any time.

**About the Remsima syringe**

**Parts of the syringe (see *Figure A*):**

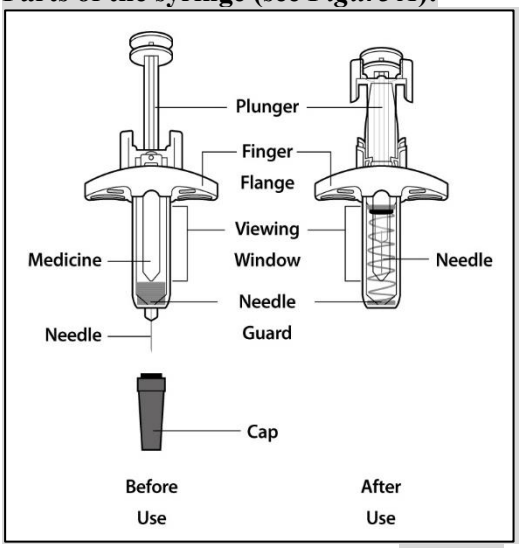


*Figure A*

- **Do not** remove the cap until you are ready to inject. Once you remove the cap, **do not** recap the syringe.

**Prepare for the injection**

**1. Gather the supplies for the injection.**

a. Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.
b. Remove the syringe from the carton stored in your refrigerator by holding the middle of the syringe body.
c. Ensure you have the following supplies:
   - Syringe
   - Alcohol swab
   - Cotton ball or gauze*
   - Adhesive bandage*
   - Sharps disposal container*

   **Items not included in the carton.*

**2. Inspect the syringe.**
**Do not** use the syringe if:

- It is cracked or damaged.
- The expiration date has passed.

**3. Inspect the medicine (see *Figure B*).**
The liquid should be clear and colourless to pale brown.
**Do not** use the syringe if the liquid is cloudy, discoloured or contains particles in it.
*Note: You may see air bubbles in the liquid. This is normal.*

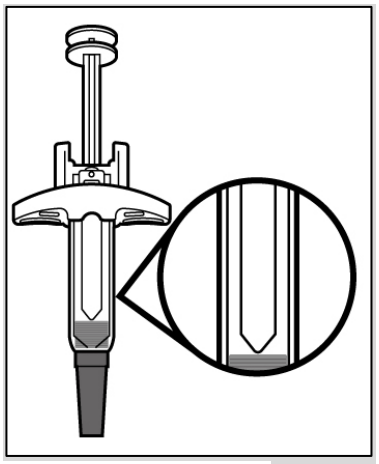

*Figure B*

**4. Wait 30 minutes.**

a. Leave the syringe at room temperature for 30 minutes to allow it to naturally warm up.

**Do not** warm the syringe using heat sources such as hot water or a microwave.

**5. Choose an injection site (see *Figure C*).**

a. Select an injection site. You may inject into:
    - The front of the thighs.
    - The abdomen except for the 5 cm around the belly button (navel).
    - The outer area of the upper arms (caregiver ONLY).

**Do not** inject into skin that is within 5 cm of your belly button (navel), or is tender, damaged, bruised, or scarred.
*Note: Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.*

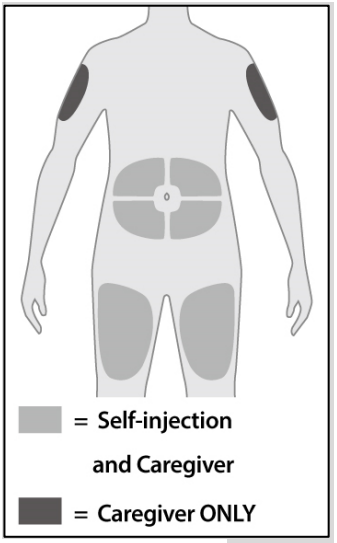


*Figure C*

**6. Wash your hands.**

a. Wash your hands with soap and water and dry them thoroughly.

**7. Clean the injection site.**

a. Clean the injection site with an alcohol swab.
b. Let the skin dry before injecting.

**Do not** blow on or touch the injection site again before giving the injection.

**Give the injection**

**8. Remove the cap (see *Figure D*).**

a. Pull the cap straight off and set it aside.

**Do not** touch the needle. Doing so may result in a needle stick injury.

*Note: It is normal to see a few drops of liquid come out of the needle upon the cap removal.*

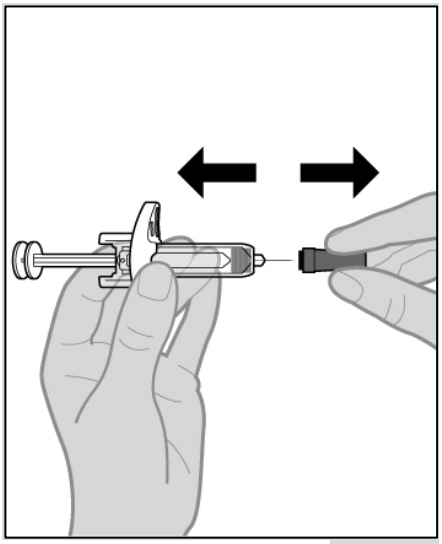

*Figure D*

**9. Insert the syringe into the injection site (see *Figure E*).**

a. Hold the syringe by its body in one hand between your thumb and index finger.
b. Using your other hand, gently pinch a fold of skin you cleaned.
c. With a quick and "dart-like" motion, insert the needle completely into the fold of the skin at a 45-degree angle.

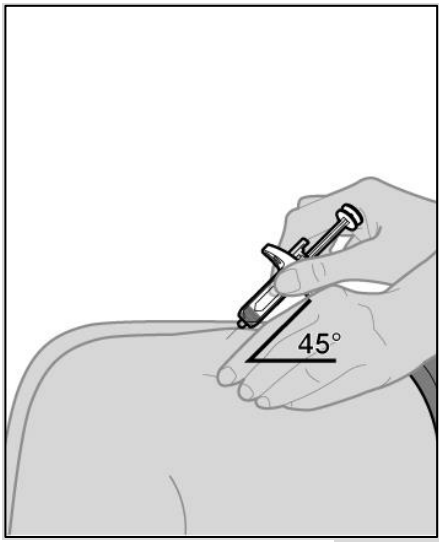


*Figure E*

**10. Give the injection (see *Figure F*).**

a. After the needle is inserted, let go of the pinched skin.
b. Push the plunger down slowly and as far as it will go until the syringe is empty.

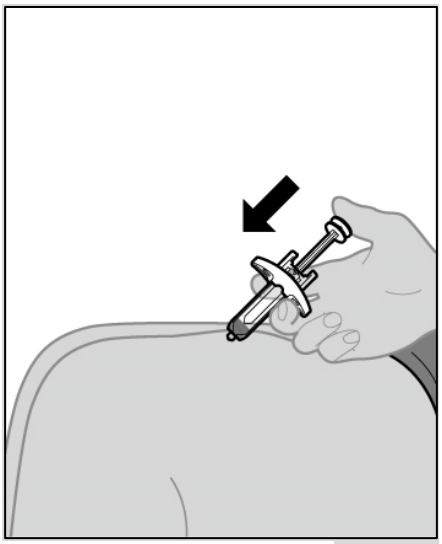

*Figure F*

**11. Remove the syringe from the injection site (see *Figure G*).**

a. After the syringe is empty, slowly lift your thumb from the plunger until needle is completely covered by the automatic needle guard.
b. Gently press a cotton ball or gauze over the injection site and hold for 10 seconds.
c. Apply an adhesive bandage, if necessary.

**Do not** rub the injection site.

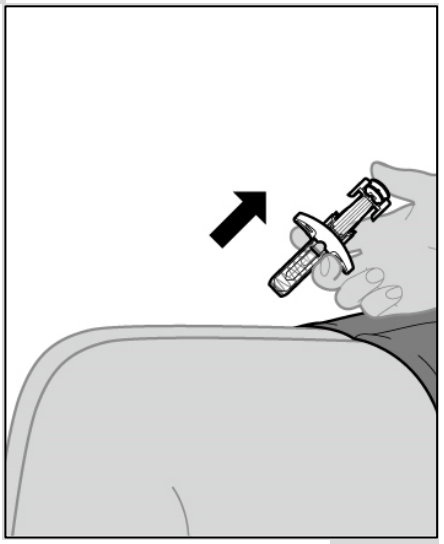

*Figure G*

**After the injection**

**12. Dispose of the syringe (see *Figure H*).**

a. Put the used syringe in an approved sharps disposal container immediately after use.
b. If you do not have an approved sharps disposal container, you may use a household container that is:
   - made of a heavy-duty plastic;
   - able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
   - upright and stable during use;
   - leak-resistant; and
   - properly labelled to warn of hazardous waste inside the container.
c. When your sharps disposal container is almost full, it should be disposed of in accordance with local requirements.

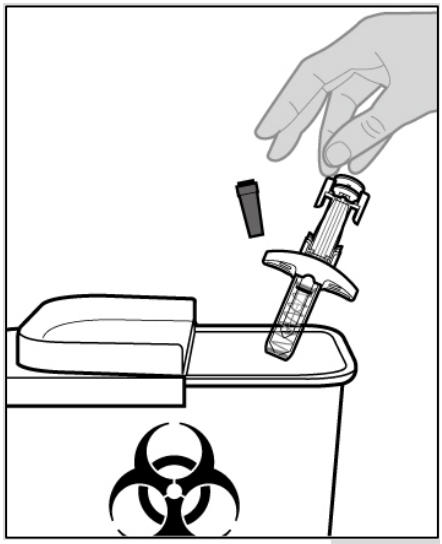

*Figure H*

**Do not** recap the syringe.

*Note: Keep the syringe and sharps disposal container out of the sight and reach of children.*

**Package leaflet: Information for the user**

**Remsima 120 mg solution for injection in pre-filled pen**
infliximab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a patient reminder card, which contains important safety information you need to be aware of before and during your treatment with Remsima.
- When starting a new card, keep this card as a reference for 4 months after your last dose of Remsima.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Remsima is and what it is used for

Remsima contains the active substance infliximab. Infliximab is a monoclonal antibody - a type of protein that attaches to a specific target in the body called TNF (tumour necrosis factor) alpha.

Remsima belongs to a group of medicines called 'TNF blockers'. It is used in adults for the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis (Bechterew's disease)
- Psoriasis
- Crohn's disease
- Ulcerative colitis.

Remsima works by selectively attaching to TNF alpha and blocking its action. TNF alpha is involved in inflammatory processes of the body so blocking it can reduce the inflammation in your body.

**Rheumatoid arthritis**
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima which you will take with another medicine called methotrexate to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Psoriatic arthritis**
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Ankylosing spondylitis (Bechterew's disease)**
Ankylosing spondylitis is an inflammatory disease of the spine. If you have ankylosing spondylitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- improve your physical function.

**Psoriasis**
Psoriasis is an inflammatory disease of the skin. If you have moderate to severe plaque psoriasis, you will first be given other medicines or treatments, such as phototherapy. If these medicines or treatments do not work well enough, you will be given Remsima to reduce the signs and symptoms of your disease.

**Ulcerative colitis**
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to treat your disease.

**Crohn's disease**
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- treat active Crohn's disease,
- reduce the number of abnormal openings (fistulae) between your bowel and your skin that have not been controlled by other medicines or surgery.

## 2. What you need to know before you use Remsima

**You must not use Remsima if**
- you are allergic to infliximab or any of the other ingredients of this medicine (listed in section 6),
- you are allergic to proteins that come from mice,
- you have tuberculosis (TB) or another serious infection such as pneumonia or sepsis (serious bacterial infection of the blood),
- you have heart failure that is moderate or severe.

Do not use Remsima if any of the above applies to you. If you are not sure, talk to your doctor before you are given Remsima.

**Warnings and precautions**
Talk to your doctor before or during treatment with Remsima if you have:

<u>Had treatment with any medicine containing infliximab before</u>

- Tell your doctor if you have had treatment with medicines containing infliximab in the past and are now starting Remsima treatment again.
- If you have had a break in your treatment with infliximab of more than 16 weeks, there is a higher risk for allergic reactions when you start the treatment again.

Local injection site reactions

- Some patients receiving infliximab via injection under the skin have experienced local injection site reactions. Signs of a local injection site reaction can include redness, pain, itching, swelling, hardness, bruising, bleeding, cold sensation, tingling sensation, irritation, rash, ulcer, hives, blisters and scab on the skin of the injection site.
- Most of these reactions are mild to moderate and mostly resolve on their own within a day.

Infections

- Tell your doctor before you are given Remsima if you have an infection even if it is a very minor one.
- Tell your doctor before you are given Remsima if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are common. These infections are caused by specific types of fungi that can affect the lungs or other parts of your body.
- You may get infections more easily when you are being treated with Remsima. If you are 65 years of age or older, you have a greater risk.
- These infections may be serious and include tuberculosis, infections caused by viruses, fungi, bacteria or other organisms in the environment and sepsis that may be life-threatening.

Tell your doctor straight away if you get signs of infection during treatment with Remsima. Signs include fever, cough, flu-like signs, feeling unwell, red or hot skin, wounds or dental problems. Your doctor may recommend temporarily stopping Remsima.

Tuberculosis (TB)

- It is very important that you tell your doctor if you have ever had TB or if you have been in close contact with someone who has had or has TB.
- Your doctor will test you to see if you have TB. Cases of TB have been reported in patients treated with infliximab, even in patients who have already been treated with medicines for TB. Your doctor will record these tests on your patient reminder card.
- If your doctor feels that you are at risk for TB, you may be treated with medicines for TB before you are given Remsima.

Tell your doctor straight away if you get signs of TB during treatment with Remsima. Signs include persistent cough, weight loss, feeling tired, fever, night sweats.

Hepatitis B virus

- Tell your doctor before you are using Remsima if you are a carrier of hepatitis B or have ever had it.
- Tell your doctor if you think you might be at risk of contracting hepatitis B.
- Your doctor should test you for hepatitis B virus.
- Treatment with TNF blockers such as Remsima may result in reactivation of hepatitis B virus in patients who carry this virus, which can be life-threatening in some cases.
- If you experience reactivation of hepatitis B, your doctor may need to stop your treatment and may give you medicines such as effective antiviral therapy with supportive treatment.

Heart problems

- Tell your doctor if you have any heart problems, such as mild heart failure.
- Your doctor will want to closely monitor your heart.

Tell your doctor straight away if you get new or worsening signs of heart failure during treatment with Remsima. Signs include shortness of breath or swelling of your feet.

Cancer and lymphoma

- Tell your doctor before you are given Remsima if you have or have ever had lymphoma (a type of blood cancer) or any other cancer.
- Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher risk of developing lymphoma.
- Patients taking Remsima may have an increased risk of developing lymphoma or another cancer.
- Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage boys or young men and most had either Crohn's disease or ulcerative colitis. This type of cancer has usually resulted in death. Almost all patients had also received medicines containing azathioprine or mercaptopurine in addition to TNF-blockers.
- Some patients treated with infliximab have developed certain kinds of skin cancer. If there are any changes in your skin or growths on the skin during or after therapy, tell your doctor.
- Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking Remsima including those over 60 years of age, your doctor may recommend regular screening for cervical cancer.

Lung disease or heavy smoking

- Tell your doctor before you are given Remsima if you have a lung disease called chronic obstructive pulmonary disease (COPD) or if you are a heavy smoker.
- Patients with COPD and patients who are heavy smokers may have a higher risk of developing cancer with Remsima treatment.

Nervous system disease

- Tell your doctor before you are given Remsima if you have or have ever had a problem that affects your nervous system. This includes multiple sclerosis, Guillain-Barré syndrome, if you have fits or have been diagnosed with 'optic neuritis'.

Tell your doctor straight away if you get symptoms of a nerve disease during treatment with Remsima. Signs include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.

Abnormal skin openings

- Tell your doctor if you have any abnormal skin openings (fistulae) before you are given Remsima.

Vaccinations

- Talk to your doctor if you recently have had or are due to have a vaccine.
- You should receive recommended vaccinations before starting Remsima treatment. You may receive some vaccines during treatment with Remsima but you should not receive live vaccines (vaccines that contain a living but weakened infectious agent) while using Remsima because they may cause infections.
- If you received Remsima while you were pregnant, your baby may also be at higher risk for getting an infection as a result of receiving a live vaccine during the first year of life. It is important that you tell your baby's doctors and other health care professionals about your Remsima use so they can decide when your baby should receive any vaccine, including live vaccines such as the BCG vaccine (used to prevent tuberculosis).
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. For more information see section on Pregnancy, breast-feeding and fertility.

Therapeutic infectious agents

- Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Operations or dental procedures

- Tell your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist that you are having treatment with Remsima by showing them your patient reminder card.

Liver problems

- Some patients receiving infliximab have developed serious liver problems.
- Tell your doctor straight away if you get symptoms of liver problems during treatment with Remsima. Signs include yellowing of the skin and eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.

Low blood counts

- In some patients receiving infliximab, the body may not make enough of the blood cells that help fight infections or help stop bleeding.
- Tell your doctor straight away if you get symptoms of low blood counts during treatment with Remsima. Signs include persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.

Immune system disorder

- Some patients receiving infliximab have developed symptoms of an immune system disorder called lupus.
- Tell your doctor straight away if you develop symptoms of lupus during treatment with Remsima. Signs include joint pain or a rash on cheeks or arms that is sensitive to the sun.

**Children and adolescents**
Do not give this medicine to children and adolescents under 18 years of age because there are no data that show that this medicine is safe and works in this age group.

**Other medicines and Remsima**
Patients who have inflammatory diseases already take medicines to treat their problem. These medicines may cause side effects. Your doctor will advise you what other medicines you must keep using while you are having Remsima.

Tell your doctor if you are using, have recently used or might use any other medicines, including any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis or medicines obtained without a prescription, such as vitamins and herbal medicines.

In particular, tell your doctor if you are using any of the following medicines:
- Medicines that affect your immune system.
- Kineret (which contains anakinra). Remsima and Kineret should not be used together.
- Orencia (which contains abatacept). Remsima and Orencia should not be used together.

While using Remsima you should not receive live vaccines. If you were using Remsima during pregnancy or if you are receiving Remsima while breast-feeding, tell your baby's doctor and other health care professionals caring for your baby about your Remsima use before the baby receives any vaccines.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Remsima.

**Pregnancy, breast-feeding and fertility**
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Remsima should only be used during pregnancy or while breast-feeding if your doctor feels it is necessary for you.
- You should avoid getting pregnant when you are being treated with Remsima and for 6 months after you stop being treated with it. Discuss the use of contraception during this time with your doctor.
- If you received Remsima during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. If you received Remsima while pregnant, giving BCG vaccine (used to prevent tuberculosis) to your baby within 12 months after birth may result in infection with serious complications, including death. Live vaccines such as the BCG vaccine should not be given to your baby within 12 months after birth, unless your baby's doctor recommends otherwise. For more information see section on vaccination.
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's doctor recommends otherwise.
- Severely decreased numbers of white blood cells have been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately.

**Driving and using machines**
Remsima is not likely to affect your ability to drive or use tools or machines. If you feel tired, dizzy, or unwell after having Remsima, do not drive or use any tools or machines.

**Remsima contains sodium and sorbitol**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free' and 45 mg sorbitol in each 120 mg dose.

**Remsima contains polysorbate 80**
This medicine contains 0.5 mg of polysorbate 80 in each pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

## 3. How to use Remsima

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

**Rheumatoid arthritis**
Your doctor will start your treatment with or without two infliximab intravenous infusion doses of 3 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). If infliximab intravenous infusion doses are given to start the treatment, they are administered 2 weeks apart via intravenous infusion. After 4 weeks from the last intravenous infusion, you will be given Remsima via injection under the skin (subcutaneous injection). If Remsima subcutaneous injection doses are given to start the treatment, Remsima 120 mg should be given as a subcutaneous injection followed by additional subcutaneous injections at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter.
The usual recommended dose of Remsima subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**Psoriatic arthritis, ankylosing spondylitis (Bechterew's disease) and psoriasis**
Your doctor will start your treatment with two infliximab intravenous infusion doses of 5 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). They are administered 2 weeks apart via intravenous infusion. After 4 weeks from the last intravenous infusion, you will be given Remsima via injection under the skin (subcutaneous injection).
The usual recommended dose of Remsima subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**Crohn's disease and ulcerative colitis**
Your doctor will start your treatment with two or three infliximab intravenous infusion doses of 5 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). They are administered 2 weeks apart via intravenous infusion and additional intravenous infusion may be given 4 weeks after the second infusion. After 4 weeks from the last intravenous infusion, you will be given Remsima via injection under the skin (subcutaneous injection).
The usual recommended dose of Remsima subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**How Remsima is given**
- Remsima 120 mg solution for injection is administered by injection under the skin (subcutaneous use) only. It is important to check the product labels to ensure that the correct formulation is being given as prescribed.
- For patients with rheumatoid arthritis, your doctor may start your Remsima treatment with or without infliximab intravenous infusion doses. For patients with ankylosing spondylitis, psoriatic arthritis or psoriasis, two infliximab intravenous infusion doses will be given to start your Remsima treatment. For patients with Crohn's disease or ulcerative colitis, two or three infliximab intravenous infusion doses will be given to start your Remsima treatment.
- For rheumatoid arthritis patients, if Remsima treatment is initiated without two infliximab intravenous infusion doses, the table below shows how often you will usually have Remsima 120 mg subcutaneous after your first dose.

| | |
|---|---|
| 2nd dose | 1 week after your 1st dose |
| 3rd dose | 2 weeks after your 1st dose |
| 4th dose | 3 weeks after your 1st dose |
| 5th dose | 4 weeks after your 1st dose |
| Further doses | 6 weeks after your 1st dose and every 2 weeks thereafter |

- Infliximab intravenous infusion doses will be given 2 weeks apart by your doctor or nurse and additional intravenous infusion may be given 4 weeks after the second infusion for Crohn's disease and ulcerative colitis patients under your doctor's discretion to start your Remsima treatment. The first Remsima subcutaneous injection will be given 4 weeks after the last intravenous infusion followed by Remsima subcutaneous injections given every 2 weeks.
- The first subcutaneous injection of Remsima will be administered under the supervision of your doctor.
- After proper training, if you feel you are well-trained and confident to inject Remsima yourself, your doctor may allow you to inject subsequent doses of Remsima yourself at home.
- Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed **"Instructions for Use"** at the end of this leaflet.

**If you use more Remsima than you should**
If you have used more Remsima than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor, pharmacist or nurse immediately. Always have the outer carton of the medicine with you, even if it is empty.

**If you forget to use Remsima**

Missed dose for up to 7 days
If you miss a dose of Remsima for up to 7 days, after the original scheduled dose, you should take the missed dose immediately. Take your next dose on the next originally planned date and then follow the original dosing schedule.

Missed dose for 8 days or more
If you miss a dose of Remsima for 8 days or more, after the original scheduled dose, you should not take the missed dose. Take your next dose on the next originally planned date and then follow the original dosing schedule.

If you are not sure when to inject Remsima, call your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However some patients may experience serious side effects and may require treatment. Side effects may also occur after your treatment with Remsima has stopped.

**Tell your doctor straight away if you notice any of the following:**
- **Signs of an allergic reaction** such as swelling of your face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions may be serious or life-threatening. An allergic reaction could happen within 2 hours of your injection or later. More signs of allergic side effects that may happen up to 12 days after your injection include pain in the muscles, fever, joint or jaw pain, sore throat or headache.
- **Signs of a local injection site reaction** such as redness, pain, itching, swelling, hardness, bruising, bleeding, cold sensation, tingling sensation, irritation, rash, ulcer, hives, blisters and scab.
- **Signs of a heart problem** such as chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea (feeling sick), vomiting, fluttering or pounding in your chest, a fast or a slow heartbeat, and swelling of your feet.
- **Signs of infection (including TB)** such as fever, feeling tired, cough which may be persistent, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, collection of pus in the gut or around the anus (abscess), dental problems or burning sensation when urinating.
- **Possible signs of cancer** including but not limited to swelling of lymph nodes, weight loss, fever, unusual skin nodules, changes in moles or skin colouring, or unusual vaginal bleeding.
- **Signs of a lung problem** such as coughing, breathing difficulties or tightness in the chest.
- **Signs of a nervous system problem (including eye problems)** such as signs of a stroke (sudden numbness or weakness of your face, arm or leg, especially on one side of your body; sudden confusion, trouble speaking or understanding; trouble seeing in one or both eyes, trouble walking, dizziness, loss of balance or coordination or a severe headache), fits, tingling/numbness in any part of your body, or weakness in arms or legs, changes in eyesight such as double vision or other eye problems.
- **Signs of a liver problem** (including hepatitis B infection when you have had hepatitis B in the past) such as yellowing of the skin or eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.
- **Signs of an immune system disorder called lupus** such as joint pain or a rash on cheeks or arms that is sensitive to the sun (lupus) or cough, shortness of breath, fever or skin rash (sarcoidosis).

- **Signs of low blood counts** such as persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.
- **Signs of serious skin problems** such as reddish-target-like spots or circular patches often with central blisters on the trunk, large areas of peeling and shedding (exfoliating) skin, ulcers of mouth, throat, nose, genitals and eyes or small pus-filled bumps that can spread over the body. These skin reactions can be accompanied by fever.

Tell your doctor straight away if you notice any of the above.

The following side effects have been observed with Remsima:

**Very common:** may affect more than 1 in 10 people
- Stomach pain, feeling sick
- Viral infections such as herpes or flu
- Upper respiratory infections such as sinusitis
- Headache
- Side effect due to an injection
- Pain.

**Common:** may affect up to 1 in 10 people
- Changes in how your liver works, increase in liver enzymes (shown in blood tests)
- Lung or chest infections such as bronchitis or pneumonia
- Difficult or painful breathing, chest pain
- Bleeding in the stomach or intestines, diarrhoea, indigestion, heartburn, constipation
- Nettle-type rash (hives), itchy rash or dry skin
- Balance problems or feeling dizzy
- Fever, increased sweating
- Circulation problems such as low or high blood pressure
- Bruising, hot flush or nosebleed, warm, red skin (flushing)
- Feeling tired or weak
- Bacterial infections such as blood poisoning, abscess or infection of the skin (cellulitis)
- Infection of the skin due to a fungus
- Blood problems such as anaemia or low white blood cell count
- Swollen lymph nodes
- Depression, problems sleeping
- Eye problems, including red eyes and infections
- Fast heart beat (tachycardia) or palpitations
- Pain in the joints, muscles or back
- Urinary tract infection
- Psoriasis, skin problems such as eczema and hair loss
- Reactions at the injection site such as pain, swelling, redness or itching
- Chills, a build-up of fluid under the skin causing swelling
- Feeling numb or having a tingling feeling.

**Uncommon:** may affect up to 1 in 100 people
- Shortage of blood supply, swelling of a vein
- Collection of blood outside the blood vessels (haematoma) or bruising
- Skin problems such as blistering, warts, abnormal skin colouration or pigmentation, or swollen lips, or thickening of the skin, or red, scaly, and flaky skin
- Severe allergic reactions (e.g. anaphylaxis), an immune system disorder called lupus, allergic reactions to foreign proteins
- Wounds taking longer to heal
- Swelling of the liver (hepatitis) or gall bladder, liver damage
- Feeling forgetful, irritable, confused, nervous

- Eye problems including blurred or reduced vision, puffy eyes or sties
- New or worsening heart failure, slow heart rate
- Fainting
- Convulsions, nerve problems
- A hole in the bowel or blockage of the intestine, stomach pain or cramps
- Swelling of your pancreas (pancreatitis)
- Fungal infections such as yeast infection, or fungal infection of the nails
- Lung problems (such as oedema)
- Fluid around the lungs (pleural effusion)
- Narrowed airway in the lungs, causing difficulty breathing
- Inflamed lining of the lung, causing sharp chest pains that feel worse with breathing (pleurisy)
- Tuberculosis
- Kidney infections
- Low platelet count, too many white blood cells
- Infections of the vagina
- Blood test result showing 'antibodies' against your own body
- Changes in cholesterol and fat levels in the blood.
- Weight gain (for most patients, the weight gain was small).

**Rare:** may affect up to 1 in 1,000 people
- A type of blood cancer (lymphoma)
- Your blood not supplying enough oxygen to your body, circulation problems such as narrowing of a blood vessel
- Inflammation of the lining of the brain (meningitis)
- Infections due to a weakened immune system
- Hepatitis B infection when you have had hepatitis B in the past
- Inflamed liver caused by a problem with the immune system (autoimmune hepatitis)
- Liver problem that causes yellowing of the skin or eyes (jaundice)
- Abnormal tissue swelling or growth
- Severe allergic reaction that may cause loss of consciousness and could be life-threatening (anaphylactic shock)
- Swelling of small blood vessels (vasculitis)
- Immune disorders that could affect the lungs, skin and lymph nodes (such as sarcoidosis)
- Collections of immune cells resulting from an inflammatory response (granulomatous lesions)
- Lack of interest or emotion
- Serious skin problems such as toxic epidermal necrolysis, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis
- Other skin problems such as erythema multiforme, blisters and peeling skin, or boils (furunculosis)
- Serious nervous system disorders such as transverse myelitis, multiple sclerosis-like disease, optic neuritis and Guillain-Barré syndrome
- Inflammation in the eye that may cause changes in the vision, including blindness
- Fluid in the lining of the heart (pericardial effusion)
- Serious lung problems (such as interstitial lung disease)
- Melanoma (a type of skin cancer)
- Cervical cancer
- Low blood counts, including a severely decreased number of white blood cells
- Small red or purple spots caused by bleeding under the skin
- Abnormal values of a blood protein called 'complement factor' which is part of the immune system
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes).

**Not known:** frequency cannot be estimated from the available data

- Cancer
- A rare blood cancer affecting mostly young men (hepatosplenic T-cell lymphoma)
- Liver failure
- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Heart attack
- Stroke
- Temporary loss of sight during or within 2 hours of infusion
- Infection due to a live vaccine because of a weakened immune system.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Remsima

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the pre-filled pen in the outer carton in order to protect from light.
- This medicine can also be stored in the original carton outside of refrigerated storage up to a maximum of 25°C for a single period of up to 28 days, but not beyond the original expiry date. In this situation, do not return to refrigerated storage again. Write the new expiry date on the carton including day/month/year. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Remsima contains**
- The active substance is infliximab. Each 1 ml single dose pre-filled pen contains 120 mg of infliximab.
- The other ingredients are acetic acid, sodium acetate trihydrate, sorbitol (E420), polysorbate 80 (E433) and water for injections.

**What Remsima looks like and contents of the pack**
Remsima is a clear to opalescent, colourless to pale brown solution which is supplied as a single use pre-filled pen.

Each pack contains 1 pre-filled pen with 2 alcohol pads, 2 pre-filled pens with 2 alcohol pads, 4 pre-filled pens with 4 alcohol pads or 6 pre-filled pens with 6 alcohol pads.

Not all pack sizes may be marketed.

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**This leaflet was last revised in {MM/YYYY}.**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

## 7. Instructions for use

Read carefully these instructions before using the Remsima pen. Consult your healthcare provider if you have questions about using the Remsima pen.

**Important information**

- Use the pen **ONLY if** your healthcare provider has trained you on the right way to prepare for and to give an injection.
- Ask your healthcare provider how often you will need to give an injection.
- Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.
- **Do not** use the pen if it has been dropped or is visibly damaged. A damaged pen may not function properly.
- **Do not** reuse the pen.
- **Do not** shake the pen at any time.

**About the Remsima pen**

**Parts of the pen (see *Figure A*):**

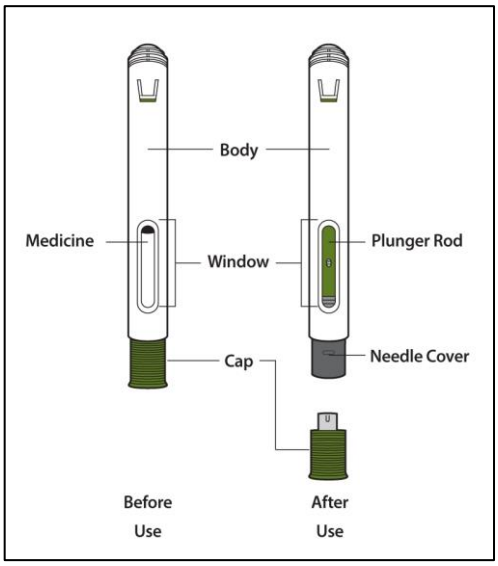


*Figure A*

- **Do not** remove the cap until you are ready to inject. Once you remove the cap, **do not** recap the pen.

**Prepare for the injection**

**1. Gather the supplies for the injection.**

a. Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.
b. Remove the pen from the carton stored in your refrigerator.
c. Ensure you have the following supplies:
   - Pen
   - Alcohol swab
   - Cotton ball or gauze*
   - Adhesive bandage*
   - Sharps disposal container*

   **Items not included in the carton.*

**2. Inspect the pen.**
**Do not** use the pen if:

- It is cracked or damaged.
- The expiration date has passed.

**3. Inspect the medicine (see *Figure B*).**
The liquid should be clear and colourless to pale brown.
**Do not** use the pen if the liquid is cloudy, discoloured or contains particles in it.
*Note: You may see air bubbles in the liquid. This is normal.*

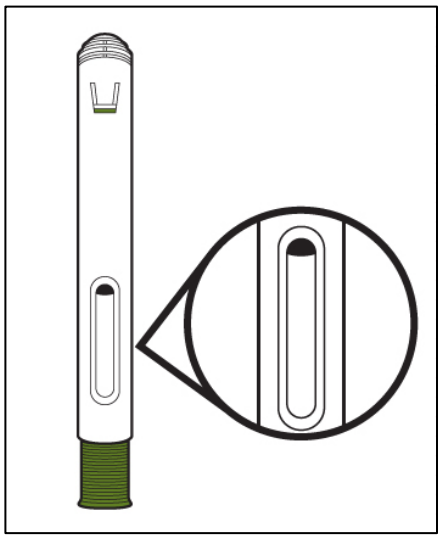

*Figure B*

**4. Wait 30 minutes.**
a. Leave the pen at room temperature for 30 minutes to allow it to naturally warm up.
**Do not** warm the pen using heat sources such as hot water or a microwave.

**5. Choose an injection site (see *Figure C*).**
a. Select an injection site. You may inject into:

- The front of the thighs.
- The abdomen except for the 5 cm around the belly button (navel).
- The outer area of the upper arms (caregiver ONLY).

**Do not** inject into skin that is within 5 cm of your belly button (navel), or is tender, damaged, bruised, or scarred.
*Note: Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.*

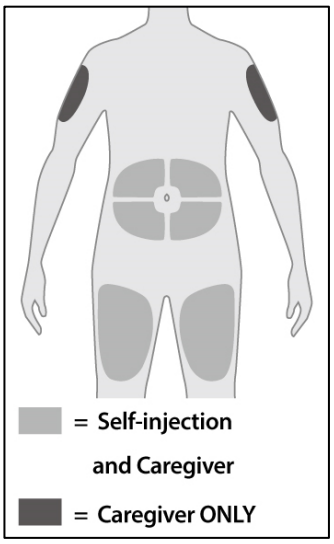


*Figure C*

**6. Wash your hands.**
a. Wash your hands with soap and water and dry them thoroughly.

**7. Clean the injection site.**
a. Clean the injection site with an alcohol swab.
b. Let the skin dry before injecting.
**Do not** blow on or touch the injection site again before giving the injection.

**Give the injection**

**8. Remove the cap (see *Figure D*).**

a. Pull the olive green cap straight off and set it aside.

**Do not** touch the needle cover. Doing so may result in a needle stick injury.

*Note: It is normal to see a few drops of liquid come out of the needle upon the cap removal.*

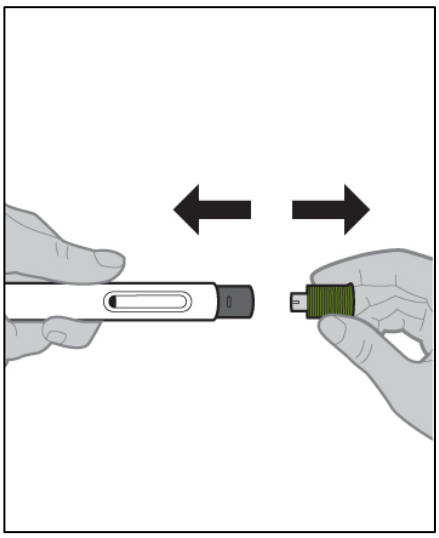

*Figure D*

**9. Place the pen on the injection site (see *Figure E*).**

a. Hold the pen so that you can see the window.

b. Without pinching or stretching the skin, place the pen over the injection site at a 90-degree angle.

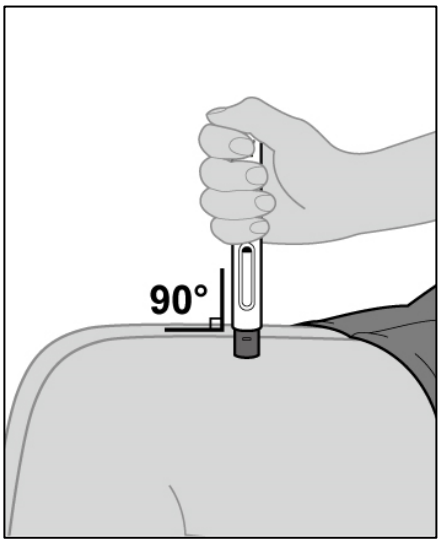


*Figure E*

**10. Start the injection (see *Figure F*).**

a. Press the pen **firmly** against the skin.

*Note: When the injection starts you will hear the 1st loud "click" and the olive green plunger rod will begin to fill the window.*

b. Keep holding the pen **firmly** against the skin and listen for the 2nd loud "click."

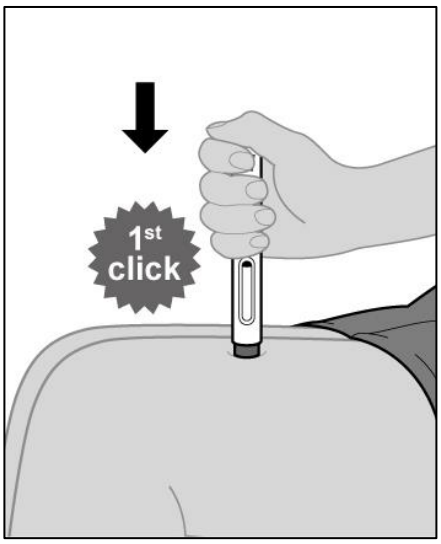


*Figure F*

**11. Finish the injection (see *Figure G*).**

a. After you hear the 2nd loud "click," **continue to hold the pen firmly against the skin and count slowly to at least five** to ensure you inject the full dose.

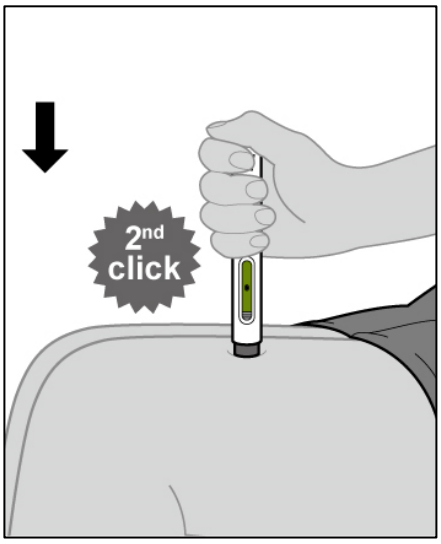


*Figure G*

**12. Remove the pen from the injection site.**

a. Look at the pen and confirm that the olive green plunger rod is filling the window completely.
b. Lift the pen from the injection site (see *Figure H*).
c. Gently press a cotton ball or gauze over the injection site and apply an adhesive bandage, if necessary.

**Do not** rub the injection site.

*Note: After you remove the pen from the injection site, the needle will be automatically covered (see Figure I).*

*Note: If the olive green plunger rod does not fill the window completely, you did not receive your full dose. Do not reuse the pen in this case. Call your healthcare provider immediately.*

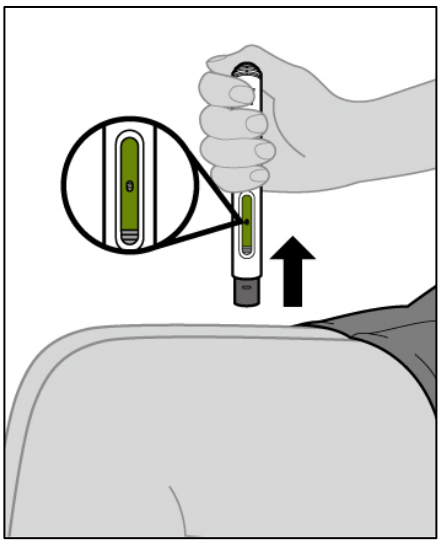

*Figure H*

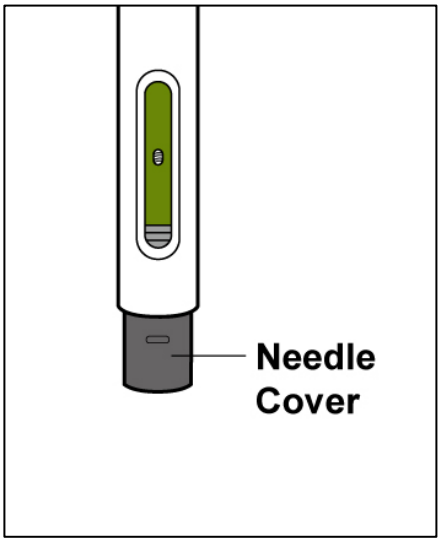


*Figure I*

**After the injection**

**13. Dispose of the pen (see *Figure J*).**

a. Put the used pen in an approved sharps disposal container immediately after use.
b. If you do not have an approved sharps disposal container, you may use a household container that is:
   - made of a heavy-duty plastic;
   - able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
   - upright and stable during use;
   - leak-resistant; and
   - properly labelled to warn of hazardous waste inside the container.
c. When your sharps disposal container is almost full, it should be disposed of in accordance with local requirements.

*Figure J*

**Do not** recap the pen.

*Note: Keep the pen and sharps disposal container out of the sight and reach of children.*

**Package leaflet: Information for the user**

**Remsima 40 mg/mL concentrate for solution for infusion**
infliximab

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a patient reminder card, which contains important safety information you need to be aware of before and during your treatment with Remsima.
- When starting a new card, keep this card as a reference for 4 months after your last dose of Remsima.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Remsima is and what it is used for

Remsima contains the active substance infliximab. Infliximab is a monoclonal antibody - a type of protein that attaches to a specific target in the body called TNF (tumour necrosis factor) alpha.

Remsima belongs to a group of medicines called 'TNF blockers'. It is used in adults for the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis (Bechterew's disease)
- Psoriasis.

Remsima is also used in adults and children 6 years of age or older for:
- Crohn's disease
- Ulcerative colitis.

Remsima works by selectively attaching to TNF alpha and blocking its action. TNF alpha is involved in inflammatory processes of the body so blocking it can reduce the inflammation in your body.

**Rheumatoid arthritis**
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima which you will take with another medicine called methotrexate to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Psoriatic arthritis**
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- slow down the damage in your joints,
- improve your physical function.

**Ankylosing spondylitis (Bechterew's disease)**
Ankylosing spondylitis is an inflammatory disease of the spine. If you have ankylosing spondylitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- reduce the signs and symptoms of your disease,
- improve your physical function.

**Psoriasis**
Psoriasis is an inflammatory disease of the skin. If you have moderate to severe plaque psoriasis, you will first be given other medicines or treatments, such as phototherapy. If these medicines or treatments do not work well enough, you will be given Remsima to reduce the signs and symptoms of your disease.

**Ulcerative colitis**
Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to treat your disease.

**Crohn's disease**
Crohn's disease is an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If these medicines do not work well enough, you will be given Remsima to:
- treat active Crohn's disease,
- reduce the number of abnormal openings (fistulae) between your bowel and your skin that have not been controlled by other medicines or surgery.

## 2. What you need to know before you use Remsima

**You must not be given Remsima if**
- you are allergic to infliximab or any of the other ingredients of this medicine (listed in section 6),
- you are allergic to proteins that come from mice,
- you have tuberculosis (TB) or another serious infection such as pneumonia or sepsis (serious bacterial infection of the blood),
- you have heart failure that is moderate or severe.
- you have hereditary fructose intolerance, a quite rare genetic condition where the enzyme for breaking down fructose is not produced.

Do not use Remsima if any of the above applies to you. If you are not sure, talk to your doctor before you are given Remsima.

**Warnings and precautions**
Talk to your doctor before or during treatment with Remsima if you have:

Had treatment with any medicine containing infliximab before

- Tell your doctor if you have had treatment with medicines containing infliximab in the past and are now starting Remsima treatment again.
- If you have had a break in your treatment with infliximab of more than 16 weeks, there is a higher risk for allergic reactions when you start the treatment again.

Infections

- Tell your doctor before you are given Remsima if you have an infection even if it is a very minor one.
- Tell your doctor before you are given Remsima if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are common. These infections are caused by specific types of fungi that can affect the lungs or other parts of your body.
- You may get infections more easily when you are being treated with Remsima. If you are 65 years of age or older, you have a greater risk.
- These infections may be serious and include tuberculosis, infections caused by viruses, fungi, bacteria or other organisms in the environment and sepsis that may be life-threatening.

Tell your doctor straight away if you get signs of infection during treatment with Remsima. Signs include fever, cough, flu-like signs, feeling unwell, red or hot skin, wounds or dental problems. Your doctor may recommend temporarily stopping Remsima.

Tuberculosis (TB)

- It is very important that you tell your doctor if you have ever had TB or if you have been in close contact with someone who has had or has TB.
- Your doctor will test you to see if you have TB. Cases of TB have been reported in patients treated with infliximab, even in patients who have already been treated with medicines for TB. Your doctor will record these tests on your patient reminder card.
- If your doctor feels that you are at risk for TB, you may be treated with medicines for TB before you are given Remsima.

Tell your doctor straight away if you get signs of TB during treatment with Remsima. Signs include persistent cough, weight loss, feeling tired, fever, night sweats.

Hepatitis B virus

- Tell your doctor before you are given Remsima if you are a carrier of hepatitis B or have ever had it.
- Tell your doctor if you think you might be at risk of contracting hepatitis B.
- Your doctor should test you for hepatitis B virus.
- Treatment with TNF blockers such as Remsima may result in reactivation of hepatitis B virus in patients who carry this virus, which can be life-threatening in some cases.
- If you experience reactivation of hepatitis B, your doctor may need to stop your treatment and may give you medicines such as effective antiviral therapy with supportive treatment.

Heart problems

- Tell your doctor if you have any heart problems, such as mild heart failure.
- Your doctor will want to closely monitor your heart.

Tell your doctor straight away if you get new or worsening signs of heart failure during treatment with Remsima. Signs include shortness of breath or swelling of your feet.

Cancer and lymphoma

- Tell your doctor before you are given Remsima if you have or have ever had lymphoma (a type of blood cancer) or any other cancer.
- Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at higher risk of developing lymphoma.
- Children and adults taking Remsima may have an increased risk of developing lymphoma or another cancer.
- Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage boys or young men and most had either Crohn's disease or ulcerative colitis. This type of cancer has usually resulted in death. Almost all patients had also received medicines containing azathioprine or mercaptopurine in addition to TNF-blockers.
- Some patients treated with infliximab have developed certain kinds of skin cancer. If there are any changes in your skin or growths on the skin during or after therapy, tell your doctor.
- Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking Remsima including those over 60 years of age, your doctor may recommend regular screening for cervical cancer.

Lung disease or heavy smoking

- Tell your doctor before you are given Remsima if you have a lung disease called chronic obstructive pulmonary disease (COPD) or if you are a heavy smoker.
- Patients with COPD and patients who are heavy smokers may have a higher risk of developing cancer with Remsima treatment.

Nervous system disease

- Tell your doctor before you are given Remsima if you have or have ever had a problem that affects your nervous system. This includes multiple sclerosis, Guillain-Barré syndrome, if you have fits or have been diagnosed with 'optic neuritis'.

Tell your doctor straight away if you get symptoms of a nerve disease during treatment with Remsima. Signs include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.

Abnormal skin openings

- Tell your doctor if you have any abnormal skin openings (fistulae) before you are given Remsima.

Vaccinations

- Talk to your doctor if you recently have had or are due to have a vaccine.
- You should receive recommended vaccinations before starting Remsima treatment. You may receive some vaccines during treatment with Remsima but you should not receive live vaccines (vaccines that contain a living but weakened infectious agent) while using Remsima because they may cause infections.
- If you received Remsima while you were pregnant, your baby may also be at higher risk for getting an infection as a result of receiving a live vaccine during the first year of life. It is important that you tell your baby's doctors and other health care professionals about your Remsima use so they can decide when your baby should receive any vaccine, including live vaccines such as the BCG vaccine (used to prevent tuberculosis).
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. For more information see section on Pregnancy, breast-feeding and fertility.

Therapeutic infectious agents

- Talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).

Operations or dental procedures

- Tell your doctor if you are going to have any operations or dental procedures.
- Tell your surgeon or dentist that you are having treatment with Remsima by showing them your patient reminder card.

Liver problems

- Some patients receiving infliximab have developed serious liver problems.
- Tell your doctor straight away if you get symptoms of liver problems during treatment with Remsima. Signs include yellowing of the skin and eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.

Low blood counts

- In some patients receiving infliximab, the body may not make enough of the blood cells that help fight infections or help stop bleeding.
- Tell your doctor straight away if you get symptoms of low blood counts during treatment with Remsima. Signs include persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.

Immune system disorder

- Some patients receiving infliximab have developed symptoms of an immune system disorder called lupus.
- Tell your doctor straight away if you develop symptoms of lupus during treatment with Remsima. Signs include joint pain or a rash on cheeks or arms that is sensitive to the sun.

**Children and adolescents**
The information above also applies to children and adolescents. In addition:

- Some children and teenage patients who have received TNF-blockers such as infliximab have developed cancers, including unusual types, which sometimes resulted in death.
- More children taking infliximab developed infections as compared to adults.
- Children should receive recommended vaccinations before starting Remsima treatment. Children may receive some vaccines during treatment with Remsima but should not receive live vaccines while using Remsima.

Remsima should only be used in children if they are being treated for Crohn's disease or ulcerative colitis. These children must be 6 years of age or older.

If you are not sure if any of the above applies to you, talk to your doctor before you are given Remsima.

**Other medicines and Remsima**
Patients who have inflammatory diseases already take medicines to treat their problem. These medicines may cause side effects. Your doctor will advise you what other medicines you must keep using while you are having Remsima.

Tell your doctor if you are using, have recently used or might use any other medicines, including any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing

spondylitis, psoriatic arthritis or psoriasis or medicines obtained without a prescription, such as vitamins and herbal medicines.

In particular, tell your doctor if you are using any of the following medicines:
- Medicines that affect your immune system.
- Kineret (which contains anakinra). Remsima and Kineret should not be used together.
- Orencia (which contains abatacept). Remsima and Orencia should not be used together.

While using Remsima you should not receive live vaccines. If you were using Remsima during pregnancy or if you are receiving Remsima while breast-feeding, tell your baby's doctor and other health care professionals caring for your baby about your Remsima use before the baby receives any vaccines.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Remsima.

**Pregnancy, breast-feeding and fertility**
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Remsima should only be used during pregnancy or while breast-feeding if your doctor feels it is necessary for you.
- You should avoid getting pregnant when you are being treated with Remsima and for 6 months after you stop being treated with it. Discuss the use of contraception during this time with your doctor.
- If you received Remsima during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. If you received Remsima while pregnant, giving BCG vaccine (used to prevent tuberculosis) to your baby within 12 months after birth may result in infection with serious complications, including death. Live vaccines such as the the BCG vaccine should not be given to your baby within 12 months after birth, unless your baby's doctor recommends otherwise. For more information see section on vaccination.
- If you are breast-feeding, it is important that you tell your baby's doctors and other healthcare professionals about your Remsima use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's doctor recommends otherwise.
- Severely decreased numbers of white blood cells have been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately.

**Driving and using machines**
Remsima is not likely to affect your ability to drive or use tools or machines. If you feel tired, dizzy, or unwell after having Remsima, do not drive or use any tools or machines.

**Remsima contains sorbitol**
Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

**Remsima contains polysorbate 80**

This medicine contains 1.3 mg of polysorbate 80 in each 100 mg vial which is equivalent to 0.5 mg/mL, and 4.4 mg of polysorbate 80 in each 350 mg vial which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

**Remsima contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before Remsima is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

## 3. How Remsima will be given

**Rheumatoid arthritis**
The usual dose is 3 mg for every kg of body weight.

**Psoriatic arthritis, ankylosing spondylitis (Bechterew's disease), psoriasis, ulcerative colitis and Crohn's disease**
The usual dose is 5 mg for every kg of body weight.

**How Remsima is given**
- Remsima will be given to you by your doctor or nurse.
- Your doctor or nurse will prepare the medicine for infusion.
- The medicine will be given as an infusion (drip) (over 2 hours) into one of your veins, usually in your arm. After the third treatment, your doctor may decide to give your dose of Remsima over 1 hour.
- You will be monitored while you are given Remsima and also for 1 to 2 hours afterwards.

**How much Remsima is given**
- The doctor will decide your dose and how often you will be given Remsima. This will depend on your disease, weight and how well you respond to Remsima.
- The table below shows how often you will usually have this medicine after your first dose.

| | |
|---|---|
| 2nd dose | 2 weeks after your 1st dose |
| 3rd dose | 6 weeks after your 1st dose |
| Further doses | Every 6 to 8 weeks depending on your disease |

**Use in children and adolescents**
In children (6 years of age or older) treated for Crohn's disease or ulcerative colitis, the recommended dose is the same as for adults.

**If you are given too much Remsima**
As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. There are no known side effects of having too much of Remsima.

**If you forget or miss your Remsima infusion**
If you forget or miss an appointment to receive Remsima, make another appointment as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However some patients may experience serious side effects and may require treatment. Side effects may also occur after your treatment with Remsima has stopped.

**Tell your doctor straight away if you notice any of the following:**

- **Signs of an allergic reaction** such as swelling of your face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions may be serious or life-threatening. An allergic reaction could happen within 2 hours of your injection or later. More signs of allergic side effects that may happen up to 12 days after your injection include pain in the muscles, fever, joint or jaw pain, sore throat or headache.
- **Signs of a heart problem** such as chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea (feeling sick), vomiting, fluttering or pounding in your chest, a fast or a slow heartbeat, and swelling of your feet.
- **Signs of infection (including TB)** such as fever, feeling tired, cough which may be persistent, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, collection of pus in the gut or around the anus (abscess), dental problems or burning sensation when urinating.
- **Possible signs of cancer** including but not limited to swelling of lymph nodes, weight loss, fever, unusual skin nodules, changes in moles or skin colouring, or unusual vaginal bleeding.
- **Signs of a lung problem** such as coughing, breathing difficulties or tightness in the chest.
- **Signs of a nervous system problem (including eye problems)** such as signs of a stroke (sudden numbness or weakness of your face, arm or leg, especially on one side of your body; sudden confusion, trouble speaking or understanding; trouble seeing in one or both eyes, trouble walking, dizziness, loss of balance or coordination or a severe headache), fits, tingling/numbness in any part of your body, or weakness in arms or legs, changes in eyesight such as double vision or other eye problems.
- **Signs of a liver problem** (including hepatitis B infection when you have had hepatitis B in the past) such as yellowing of the skin or eyes, dark-brown coloured urine, pain or swelling in the upper right side of the stomach area, joint pain, skin rashes, or fever.
- **Signs of an immune system disorder called lupus** such as joint pain or a rash on cheeks or arms that is sensitive to the sun (lupus) or cough, shortness of breath, fever or skin rash (sarcoidosis).
- **Signs of low blood counts** such as persistent fever, bleeding or bruising more easily, small red or purple spots caused by bleeding under the skin, or looking pale.
- **Signs of serious skin problems** such as reddish-target-like spots or circular patches often with central blisters on the trunk, large areas of peeling and shedding (exfoliating) skin, ulcers of mouth, throat, nose, genitals and eyes or small pus-filled bumps that can spread over the body. These skin reactions can be accompanied by fever.

Tell your doctor straight away if you notice any of the above.

The following side effects have been observed with Remsima:

**Very common:** may affect more than 1 in 10 people

- Stomach pain, feeling sick
- Viral infections such as herpes or flu
- Upper respiratory infections such as sinusitis
- Headache
- Side effect due to an infusion
- Pain.

**Common:** may affect up to 1 in 10 people

- Changes in how your liver works, increase in liver enzymes (shown in blood tests)
- Lung or chest infections such as bronchitis or pneumonia
- Difficult or painful breathing, chest pain
- Bleeding in the stomach or intestines, diarrhoea, indigestion, heartburn, constipation
- Nettle-type rash (hives), itchy rash or dry skin
- Balance problems or feeling dizzy
- Fever, increased sweating
- Circulation problems such as low or high blood pressure
- Bruising, hot flush or nosebleed, warm, red skin (flushing)
- Feeling tired or weak
- Bacterial infections such as blood poisoning, abscess or infection of the skin (cellulitis)
- Infection of the skin due to a fungus
- Blood problems such as anaemia or low white blood cell count
- Swollen lymph nodes
- Depression, problems sleeping
- Eye problems, including red eyes and infections
- Fast heart beat (tachycardia) or palpitations
- Pain in the joints, muscles or back
- Urinary tract infection
- Psoriasis, skin problems such as eczema and hair loss
- Reactions at the injection site such as pain, swelling, redness or itching
- Chills, a build-up of fluid under the skin causing swelling
- Feeling numb or having a tingling feeling.

**Uncommon:** may affect up to 1 in 100 people

- Shortage of blood supply, swelling of a vein
- Collection of blood outside the blood vessels (haematoma) or bruising
- Skin problems such as blistering, warts, abnormal skin colouration or pigmentation, or swollen lips, or thickening of the skin, or red, scaly, and flaky skin
- Severe allergic reactions (e.g. anaphylaxis), an immune system disorder called lupus, allergic reactions to foreign proteins
- Wounds taking longer to heal
- Swelling of the liver (hepatitis) or gall bladder, liver damage
- Feeling forgetful, irritable, confused, nervous
- Eye problems including blurred or reduced vision, puffy eyes or sties
- New or worsening heart failure, slow heart rate
- Fainting
- Convulsions, nerve problems
- A hole in the bowel or blockage of the intestine, stomach pain or cramps
- Swelling of your pancreas (pancreatitis)
- Fungal infections such as yeast infection, or fungal infection of the nails
- Lung problems (such as oedema)
- Fluid around the lungs (pleural effusion)
- Narrowed airway in the lungs, causing difficulty breathing
- Inflamed lining of the lung, causing sharp chest pains that feel worse with breathing (pleurisy)
- Tuberculosis
- Kidney infections
- Low platelet count, too many white blood cells
- Infections of the vagina
- Blood test result showing ‘antibodies’ against your own body.
- Changes in cholesterol and fat levels in the blood.
- Weight gain (for most patients, the weight gain was small).

**Rare:** may affect up to 1 in 1,000 people
- A type of blood cancer (lymphoma)
- Your blood not supplying enough oxygen to your body, circulation problems such as narrowing of a blood vessel
- Inflammation of the lining of the brain (meningitis)
- Infections due to a weakened immune system
- Hepatitis B infection when you have had hepatitis B in the past
- Inflamed liver caused by a problem with the immune system (autoimmune hepatitis)
- Liver problem that causes yellowing of the skin or eyes (jaundice)
- Abnormal tissue swelling or growth
- Severe allergic reaction that may cause loss of consciousness and could be life-threatening (anaphylactic shock)
- Swelling of small blood vessels (vasculitis)
- Immune disorders that could affect the lungs, skin and lymph nodes (such as sarcoidosis)
- Collections of immune cells resulting from an inflammatory response (granulomatous lesions)
- Lack of interest or emotion
- Serious skin problems such as toxic epidermal necrolysis, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis
- Other skin problems such as erythema multiforme, blisters and peeling skin, or boils (furunculosis)
- Serious nervous system disorders such as transverse myelitis, multiple sclerosis-like disease, optic neuritis and Guillain-Barré syndrome
- Inflammation in the eye that may cause changes in the vision, including blindness
- Fluid in the lining of the heart (pericardial effusion)
- Serious lung problems (such as interstitial lung disease)
- Melanoma (a type of skin cancer)
- Cervical cancer
- Low blood counts, including a severely decreased number of white blood cells
- Small red or purple spots caused by bleeding under the skin
- Abnormal values of a blood protein called 'complement factor' which is part of the immune system
- Lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes).

**Not known:** frequency cannot be estimated from the available data
- Cancer in children and adults
- A rare blood cancer affecting mostly teenage boys or young men (hepatosplenic T-cell lymphoma)
- Liver failure
- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin.
- Worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Heart attack
- Stroke
- Temporary loss of sight during or within 2 hours of infusion
- Infection due to a live vaccine because of a weakened immune system.

**Additional side effects in children and adolescents**
Children who took infliximab for Crohn's disease showed some differences in side effects compared with adults who took infliximab for Crohn's disease. The side effects that happened more in children were: low red blood cells (anaemia), blood in stool, low overall levels of white blood cells (leukopenia), redness or blushing (flushing), viral infections, low levels of white blood cells that

fight infection (neutropenia), bone fracture, bacterial infection and allergic reactions of the breathing tract.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Remsima

Remsima will generally be stored by the health professionals. The storage details should you need them are as follows:
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C – 8°C).
- This medicine can also be stored in the original carton outside of refrigerated storage up to a maximum of 30°C for a single period of up to 15 days, but not beyond the original expiry date. In this situation, do not return to refrigerated storage again. Write the new expiry date on the carton including day/month/year. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- It is recommended that when Remsima is prepared for infusion, it is used as soon as possible (within 3 hours). However, if the solution is prepared in germ-free conditions, it can be stored in a refrigerator at 2°C – 8°C up to 60 days and for an additional 24 hours at 30 °C after removal from the refrigerator.
- Do not use this medicine if it is discoloured or if there are particles present.

## 6. Contents of the pack and other information

**What Remsima contains**
- The active substance is infliximab. Each vial contains 100 mg or 350 mg of infliximab, and each mL contains 40 mg of infliximab.
- The other ingredients are acetic acid, sodium acetate trihydrate, sorbitol (E420), polysorbate 80 (E433), water for injections.

**What Remsima looks like and contents of the pack**
Remsima is supplied as a glass vial containing concentrate for solution for infusion. Remsima is a clear to opalescent solution, colourless to pale brown liquid.

Remsima is produced in packs of 1, 2, 3, 4 or 5 vials. Not all pack sizes may be marketed.

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**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

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The following information is intended for healthcare professionals only:

Patients treated with Remsima should be given the patient reminder card.

**Instructions for use and handling – storage conditions**

Store at 2°C – 8°C.

Remsima may be stored at temperatures up to a maximum of 30°C for a single period of up to 15 days, but not exceeding the original expiry date. The new expiry date must be written on the carton. Upon removal from refrigerated storage, Remsima must not be returned to refrigerated storage.

**Instructions for use and handling –dilution and administration**

In order to improve the traceability of biological medicinal products, the name and batch number of the administered medicinal product should be clearly recorded.

1. The dose and the number of Remsima vials have to be calculated. Each Remsima vial contains either 100 mg or 350 mg infliximab. The required total volume of Remsima concentrate has to be calculated.

2. The required volume of the Remsima concentrate should be withdrawn aseptically and diluted to 250 mL with sodium chloride 9 mg/mL (0.9%) solution for infusion. Do not dilute the Remsima concentrate with any other diluent. The dilution can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250 mL glass bottle or infusion bag equal to the required volume of Remsima concentrate. The required volume of Remsima concentrate should slowly be added to the 250-mL infusion bottle or bag and gently be mixed. For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL , 1000 mL ) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/ mL. If stored refrigerated after dilution, the infusion solution must be allowed to equilibrate at room temperature (up to 30°C) for 3 hours prior to Step 3 (infusion).

3. The infusion solution has to be administered over a period of not less than the infusion time recommended (see section 3). Only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometre or less) should be used. Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of dilution. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has been taken place in controlled and validated aseptic conditions. Any unused portion of the infusion solution should not be stored for reuse.

4. Remsima should be visually inspected for particulate matter or discolouration prior to administration. If visibly opaque particles, discolouration or foreign particles are observed it should not be used.

5. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.