The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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EMEA PUBLIC STATEMENT ON INFLIXIMAB (REMICADE)
- reports of tuberculosis infections -

The EMEA's scientific committee CPMP has been made aware of 28 post-marketing reports of tuberculosis (TB), in patients treated with infliximab (Remicade).

Infliximab is a chimeric human-murine monoclonal antibody that binds to and thereby inhibits the biological activity of tumour necrosis factor aplha (TNFα). Remicade was first approved in the USA in August 1998. Within the European Union, a marketing authorisation was issued in August 1999 for the treatment of severe, active Crohn's disease or of fistulising Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment such as a corticosteroid and/or an immunosuppressant. In June 2000, Remicade received additional approval for reducing the signs and symptoms of active rheumatoid arthritis in patients whose response to disease-modifying drugs, including methotrexate, has been inadequate.

Since the first marketing in the USA in August 1998, an estimated 100 000 patients have been treated with the product worldwide.

To date, 28 cases of TB have been reported (9 cases in North America and 19 cases in Europe), of which one had a fatal outcome. Some of these have been miliary tuberculosis and some have been of unusual extrapulmonary location. The majority of patients had a prior history of treatment with immunosuppressants and corticosteroids and in a significant proportion, the onset of active TB occurred after three or less infusions of Remicade, thus supporting a possible relationship with initiation of Remicade therapy. As clinical experience with Remicade is still limited, the onset (or re-activation) of TB or of other opportunistic infections also after a longer period of treatment cannot be ruled out.

The approved Summary of Product Characteristics (SPC) currently contraindicates the use of Remicade in clinically serious infections. It also warns of the known risks of exacerbating infections through the inhibition of TNF-alpha, which is an important mediator of inflammation and cellular immune responses.

In view of the seriousness of these reports, the EMEA also wishes to draw the attention to the following recommendations:

- **If active tuberculosis is suspected, Remicade treatment should be stopped until the diagnosis is ruled out or the infection has been treated in accordance with current guidelines.**

- **Before starting treatment with Remicade, patients should be evaluated for both active and inactive ('latent') tuberculosis, by way of a detailed medical history that includes personal history of tuberculosis or possible previous contact with tuberculosis and consideration of appropriate screening tests (chest x-ray, tuberculin test). Prescribers are reminded that false negative tuberculin test results may be obtained in patients who are severely ill or immuno-suppressed. If inactive ('latent') tuberculosis is diagnosed, measures should be taken to prevent the activation of tuberculosis and the risk / benefit for the patient should be considered before starting Remicade therapy.**

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- **Patients should also be instructed to seek medical advice if signs and / or symptoms suggestive of tuberculosis (e.g. persistent cough, wasting / weight loss, low-grade fever) appear.**

As an urgent measure, the patient and prescribing information has been amended accordingly through a rapid procedure at the request of the marketing authorisation holder. The EMEA thought it necessary to provide this new information to the public.

The revised sections of the Summary of Product Characteristics and of the patient leaflet are attached for more detailed information. The complete revised product information is available in the updated European Public Assessment Report of Remicade published on the EMEA website

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Revised sections 4.3, 4.4 and 4.8 of the SPC and section 2 of the Package Leaflet

(The relevant parts are highlighted in bold)

4.3 Contraindications

Remicade is contraindicated in patients with severe infections such as sepsis, abscesses, tuberculosis and opportunistic infections (see section 4.4).

Remicade must not be given to patients with a history of hypersensitivity to infliximab (see section 4.8), to other murine proteins or to any of the excipients.

4.4 Special warnings and special precautions for use

Infusion reactions and hypersensitivity
Infliximab has been associated with acute infusion effects and a delayed hypersensitivity reaction. These differ in their time of onset.

Acute infusion reactions may develop during or within 2 hours of infusion and are most likely to occur during the first and second infusion. These effects may be related to the rate of infusion of infliximab. If acute infusion reactions occur, the infusion rate can be reduced or the infusion temporarily interrupted until symptoms subside and then restarted at a slower rate. Mild and transient effects require no medical treatment or discontinuation of the infusion. Some effects can be moderate to severe and may require symptomatic treatment and considerations to discontinue infliximab infusion must be made. Emergency equipment and medications for the treatment of these effects (e.g., paracetamol, antihistamines, corticosteroids and/or adrenaline) must be available for immediate use. Patients may be pretreated with e.g., antihistamine and/or paracetamol to prevent mild and transient effects.

Antibodies directed towards infliximab (previously referred to as human antichimeric antibodies, HACA) will develop in some patients and rarely may cause serious allergic reactions. Patients who are intolerant to methotrexate or other non-corticosteroid immunosuppressants (such as azathioprine, 6-mercaptopurine) and discontinue immunosuppressants prior to or during Remicade treatment potentially are at greater risk in developing these antibodies (see section 4.8: “Immunogenicity”). These antibodies can not always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and Remicade must be discontinued.

A delayed hypersensitivity reaction has been observed in a significant number of patients with Crohn’s disease (25%) who were retreated with infliximab following a 2 to 4 year period without infliximab treatment. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. Advise patients to seek immediate medical advice if they experience any delayed adverse event (see section 4.8: “Delayed hypersensitivity”). If patients are retreated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections
Tumour necrosis factor alpha (TNFα) mediates inflammation and modulates cellular immune responses. **Opportunistic infections have been reported in patients treated with infliximab, suggesting that host defence against infections is compromised. It should be noted that suppression of TNFα may also mask symptoms of infection such as fever.**

Patients must be monitored closely for infections while on and after treatment with Remicade. Because the elimination of infliximab may take up to six months, a close monitoring of the patients throughout this period is important. **Treatment with Remicade must be stopped if a patient develops a serious infection or sepsis.**

Cases of active tuberculosis including miliary tuberculosis and some with unusual extrapulmonary location have been reported in patients treated with Remicade. If active tuberculosis is suspected,

Remicade treatment should be stopped until the diagnosis is ruled out or the infection has been treated in accordance with current guidelines.

Before starting treatment with Remicade, patients should be evaluated for both active and inactive ('latent') tuberculosis, by way of a detailed medical history that includes personal history of tuberculosis or possible previous contact with tuberculosis and consideration of appropriate screening tests (chest x-ray, tuberculin test). Prescribers are reminded that false negative tuberculin test results may be obtained in patients who are severely ill or immuno-suppressed. If inactive ('latent') tuberculosis is diagnosed, measures should be taken to prevent the activation of tuberculosis and the risk / benefit for the patient should be considered before starting Remicade therapy.

When on Remicade treatment, 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.

If a patient requires surgery while on infliximab therapy, appropriate precautions must be taken as necessary.

Autoimmune processes
The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process in a subgroup of genetically susceptible patients. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Remicade and is positive for antibodies against double-stranded DNA, treatment must be discontinued (see section 4.8: "Anti-nuclear antibodies (ANA)/Double-stranded DNA (dsDNA) antibodies").

Others
Treatment with Remicade in children 0-17 years with rheumatoid arthritis or Crohn's disease has not been studied. Until safety and efficacy data in children are available, such treatment is to be avoided.

The pharmacokinetics of infliximab in elderly patients has not been studied. Studies have not been performed in patients with liver or renal disease (see section 5.2 Pharmacokinetic properties).

There are not sufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see section 5.3).

There is limited safety experience of Remicade treatment in patients who have undergone arthroplasty.

4.8 Undesirable effects

In clinical studies with infliximab, adverse drug reactions (ADRs) reasonably attributable to treatment were observed in 57% of infliximab-treated patients and 36% of placebo-treated patients. Reasonably-related ADRs are listed in Table 1 by system organ class and frequency (common > 1/100, < 1/10; uncommon > 1/1000, < 1/100). Frequency is based on the excess incidence of the ADR compared with placebo in pooled data from clinical studies involving 192 patients receiving placebo and 771 patients receiving infliximab (primarily rheumatoid arthritis and Crohn's disease patients). Most ADRs were mild to moderate in severity, and the most frequently affected system organ classes were the respiratory, and skin and appendages. The most common causes for discontinuation of treatment were dyspnoea, urticaria and headache.

Table 1
Undesirable Effects in Clinical Studies

Resistance mechanism	
Common:	Viral infection (e.g. influenza, herpes infections), fever
Uncommon:	Abscess, cellulitis, moniliasis, sepsis, impaired healing, bacterial infection, **tuberculosis,** fungal infection
Immune	
Uncommon:	Autoantibodies, lupus-like syndrome, complement factor abnormality
Blood	
Uncommon:	Anaemia, leukopoenia, lymphadenopathy, lymphocytosis, lymphopoenia, neutropoenia, thrombocytopoenia
Psychiatric	
Uncommon:	Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence
Central and peripheral nervous system	
Common:	Headache, vertigo/dizziness
Vision and hearing	
Uncommon:	Conjunctivitis, endophthalmitis, keratoconjunctivitis
Cardiovascular	
Common:	Flushing
Uncommon:	Ecchymosis/haematoma, hypertension, hypotension, syncope, petechia, thrombophleblitis, bradycardia, palpitation, vasospasm, cyanosis, peripheral ischaemia, arrythmia
Respiratory system	
Common:	Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea
Uncommon:	Sinusitis, epistaxis, bronchospasm, pleurisy, respiratory tract allergic reaction, pulmonary oedema
Gastro-intestinal system	
Common:	Nausea, diarrhoea, abdominal pain, dyspepsia
Uncommon:	Constipation, gastroesophageal reflux, cheilitis, diverticulitis
Liver and biliary system	
Common:	Abnormal hepatic function
Uncommon:	Cholecystitis
Skin and appendages	
Common:	Rash, pruritus, urticaria, increased sweating, dry skin
Uncommon:	Fungal dermatitis/ onychomycosis, eczema/ seborrhoea, hordeolum, bullous eruption, furunculosis, periorbital oedema, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/coloration, alopoecia
Musculo-skeletal system	
Uncommon:	Myalgia, arthralgia
Urinary system	
Uncommon:	Urinary tract infection, pyelonephritis
Reproductive	
Uncommon:	Vaginitis
Body as a whole-general	
Common:	Fatigue, chest pain
Uncommon:	Oedema, hot flushes, infusion syndrome, pain, chills/rigors
Administration/application site	
Uncommon:	Injection site reactions

Infusion-related effects: In clinical studies, 19% of infliximab-treated patients compared with 8% of placebo-treated patients experienced an infusion-related effect during infusion or within 2 hours post infusion. Approximately 3% of infusions were accompanied by non-specific symptoms such as fever or chills, 0.7% were accompanied by pruritus or urticaria, 1% were accompanied by cardiopulmonary reactions (primary chest pain, hypotension, hypertension or dyspnoea), and 0.1% were accompanied by combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Discontinuation of treatment resulted in 1.9% of patients, and all patients recovered with or without medical therapy. Infusion-related effects in patients were more likely to occur during the first (8%) and less likely on subsequent infusions (second, 7%; third, 6%; and fourth, 4%; etc.).

Delayed hypersensitivity: In a clinical study of 40 patients retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. No similar set of delayed adverse events has been observed in any other clinical study involving a total of 771 patients receiving 4797 infusions with intervals predominantly of 14 weeks or less, but ranging from 1 to 55 weeks. In ongoing studies and post-marketing reports, these events have been rare and have occurred at intervals of less than 1 year.

Immunogenicity: Patients who developed antibodies to infliximab were more likely to develop 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 47 of 199 (24%) patients with any immunosuppressant therapy, and in 33 of 90 (37%) patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 6 of 77 (8%) patients developed antibodies to infliximab. Due to methodological shortcomings, 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.

Infections: In clinical studies 32% of infliximab-treated patients experienced infections compared with 22% of placebo-treated patients. Serious infections, such as pneumonia, were reported in 5% of both infliximab-treated patients and placebo-treated patients (see section 4.4).
In post marketing surveillance, opportunistic infections such as tuberculosis, pneumocystis carinii pneumonia (PCP), histoplasmosis, coccidioidomycosis, aspergillosis and oesophageal candidiasis have been reported.

Lymphoproliferative disorders: In clinical studies with infliximab and during long-term follow-up of three years, representing 1385 patient years, four cases of lymphomas and 10 other malignancies were detected as compared with one malignancy in placebo-treated patients observed during 189 patient years. These observed rates and incidences were similar to those expected for the populations studied. It is unknown if chronic exposure to infliximab can increase the incidence of these disorders. The long-term immunosuppressive effects of concomitant use of methotrexate and infliximab are to be considered.

Antinuclear antibodies (ANA)/Double-stranded DNA (dsDNA) antibodies: In clinical studies infliximab-treated patients positive for ANA increased from 43% pre-treatment to 57% at the last evaluation. Anti-dsDNA antibodies developed in approximately 17% of patients treated with infliximab. Clinical signs consistent with a lupus-like syndrome have developed rarely. Normalisation of anti-dsDNA levels occurred after discontinuation of infliximab therapy.

2. BEFORE YOU USE REMICADE

[List of information necessary before taking the medicinal product]

[Contraindications]

Do not use Remicade:

if you have a history of a serious hypersensitivity or allergy to any ingredient of the product or to mouse (murine) proteins or if you have an infection or abscess. You must discuss this with your doctor.

[Appropriate precautions for use; special warnings]

Take special care with Remicade:

Treatment with Remicade in children 0-17 years with rheumatoid arthritis or Crohn's disease has not been studied. Until safety and efficacy data in children are available, such treatment is to be avoided.

Specific studies with Remicade have not been conducted in elderly patients, or in patients with hepatic or renal disease.

Some patients had allergic reactions within 2 hours of receiving Remicade. These reactions were generally mild to moderate; however, on rare occasions they were more severe. The symptoms of such reactions were most often skin rash, hives, fatigue, wheezing, difficulty in breathing and/or low blood pressure. The symptoms will most often occur the first and second time you get the medicine. If you notice these symptoms tell your doctor. If the symptoms occur during your infusion, your doctor may slow down the speed of the infusion so that it will take longer for you to get your medicine. Your doctor may also stop giving the medicine until the symptoms go away and then begin giving the medicine again. Your doctor may also treat your symptoms with other medicines (paracetamol, antihistamines, corticosteroids, bronchodilators and/or adrenaline). Most of the time you can still get Remicade even if the symptoms occur. However, in some cases your doctor may decide that it is best not to give you Remicade anymore.

Taking Remicade again after a drug free period of more than 14 weeks is not recommended.

If your last Remicade dose was given to you 2 years ago or more and you are given Remicade again, it is possible that you might have an allergic reaction 3 to 12 days after your infusion. The reaction can be serious. Signs and symptoms are tenderness or pain in the muscles, rash, fever, joint or jaw pain, hand and face swelling, swallowing difficulties, itching, sore throat and/or headache. Contact your doctor immediately for treatment of these symptoms.

You might get infections more easily. Some cases of tuberculosis have been reported in patients treated with Remicade. Before starting Remicade, it is important to tell your doctor if you have ever had, or been in close contact with tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, fever), or any other infection appear during therapy notify your doctor immediately.

On rare occasions, you may develop signs and symptoms of a disease called lupus (persistent rash, fever, joint pain and tiredness). If these symptoms occur and blood tests indicate that this may be happening, Remicade treatment will be stopped. With the appropriate treatment, the symptoms will generally disappear.

Generally, patients who have rheumatoid arthritis or Crohn's disease take several medicines which themselves may cause side effects. If you get additional side effects or any new symptoms, please tell your doctor.