ANNEX I
SUMMARY OF PRODUCT OF ROTERISTICS

We dicinal product no ways and the second s

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

# 1. NAME OF THE MEDICINAL PRODUCT

LIFMIOR 25 mg powder and solvent for solution for injection.

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by scott binant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human tgG1. This Fc component contains the hinge, CH<sub>2</sub> and CH<sub>3</sub> regions, but not the CH<sub>1</sub> region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is 1.7 x 10<sup>6</sup> units/mg.

For the full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (powd r for injection).

The powder is white. The solvent is a clear, colourless liquid.

#### 4. CLINICAL PARTICULARS

# 4.1 Therapeutic indications

#### Rheumatoid arthritis

LIFMIOR in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless convaindicated), has been inadequate.

LIFMIOR can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with nethotrexate is inappropriate.

LIFMIOI is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in a un not previously treated with methotrexate.

LIFMIOR, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

# Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

LIFMIOR has not been studied in children aged less than 2 years.

# Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. LIFMIOR 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.

# Axial spondyloarthritis

# Ankylosing spondylitis (AS)

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

# Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or hag etic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal acti-inflammatory drugs (NSAIDs).

# Plaque psoriasis

Treatment of adults with moderate to severe plaque psorias, who failed to respond to, or who have a contraindication to, or are intolerant to other systemic merapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

# Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis archildren and adolescents from the age of 6 years who are inadequately controlled by, or are intelerant to, other systemic therapies or phototherapies.

# 4.2 Posology and method of administration

LIFMIOR treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of theumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitic non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patient treate with LIFMIOR should be given the Patient Alert Card.

LIFMIOR is available in strengths of 10, 25 and 50 mg.

#### Posology

#### hermatoid arthritis

25 kg LIFMIOR administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis

The recommended dose is 25 mg LIFMIOR administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

# Plaque psoriasis

The recommended dose of LIFMIOR is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with LIFMIOR should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with LIFMIOR is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

# Special populations

Renal and hepatic impairment No dose adjustment is required.

#### **Elderly**

No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

# Paediatric population

# Juvenile idiopathic arthritis

The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg ptr dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses roughing/kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatments should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be more appropriate for administration to children with JIA below the weight of 25 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1):

There is generally no applicable accord LIFMIOR in children aged below 2 years in the indication juvenile idiopathic arthritic.

Paediatric plaque pso lasil (age 6 years and above)

The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Tream en should be discontinued in patients who show no response after 12 weeks.

If re-treat tent with LIFMIOR is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

Where is generally no applicable use of LIFMIOR in children aged below 6 years in the indication plante psoriasis.

# Method of administration

LIFMIOR is administered by subcutaneous injection. LIFMIOR powder for solution must be reconstituted in 1 ml of solvent before use (see section 6.6).

Comprehensive instructions for the preparation and administration of the reconstituted LIFMIOR vial are given in the package leaflet, section 7, "Instructions for preparation and giving an injection of LIFMIOR."

# 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with LIFMIOR should not be initiated in patients with active infections, including chronic or localised infections.

# 4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

#### Infections

Patients should be evaluated for infections before, during, and after treatment with LIEM ON, taking into consideration that the mean elimination half-life of etanercept is approximately 70 rours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of LMMIOR (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and paralites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with LIFMIOR should be monitored closely. Administration of LIFMIOR should be discentified if a patient develops a serious infection. The safety and efficacy of LIFMIOR in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of LIFMIOR in patients with a history of recurring or chronic infections or with urderlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

#### **Tuberculosis**

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with LIFMIOR.

Before starting treatment with LIFMIOR, 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 appreciable previous contact with tuberculosis and previous and/or current immunosuppreciable therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, 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's alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or tunnocompromised.

If active tuberculosis is diagnosed, LIFMIOR therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of LIFMIOR, and in accordance with local recommendations. In this situation, the benefit/risk balance of LIFMIOR therapy should be very carefully considered. 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 LIFMIOR treatment.

# Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including LIFMIOR, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with LIFMIOR. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering LIFMIOR in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, LIFMIOR should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

# Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving LIFMIOR. LIFMIOR should be used with caution in patients with a history of hepatitis C.

# Concurrent treatment with anakinra

Concurrent administration of LIFMIOR and anakinra has been associated with an increased risk of serious infections and neutropenia compared to LIFMIOR alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of LIFMIOR anakinra is not recommended (see sections 4.5 and 4.8).

# Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and LLMIOR resulted in increased incidences of serious adverse events. This combination has not remonstrated increased clinical benefit; such use is not recommended (see section 4.5).

# Allergic reactions

Allergic reactions associated with LIFMIOR administration have been reported commonly. Allergic reactions have included angioedema and un caria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, LIFNYOR therapy should be discontinued immediately and appropriate therapy initiated.

# **Immunosuppression**

The possibility exists for TNF degonists, including LIFMIOR, to affect host defences against infections and malignancies inc. TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with LIFMIOR, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile id or athritis patients developed varicella infection and signs and symptoms of aseptic maningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus the locemporarily discontinue LIFMIOR therapy and be considered for prophylactic treatment with Var cella Zoster Immune Globulin.

The safety and efficacy of LIFMIOR in patients with immunosuppression have not been evaluated.

# Malignancies and lymphoproliferative disorders

*Solid and haematopoietic malignancies (excluding skin cancers)* 

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients

receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. 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.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy  $\leq$  18 years of age), including LIFMIOR, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

#### Skin cancers

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patient treated with TNF-antagonists, including LIFMIOR. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with LIFMIOR. Periodic sline experiments recommended for all patients, particularly those with risk factors for skin calcer.

Combining the results of controlled clinical trials, more cases of notice were observed in patients receiving LIFMIOR compared with control patients, particularly in patients with psoriasis.

# Vaccinations

Live vaccines should not be given concurrently with LKMIOR. No data are available on the secondary transmission of infection by live vaccines in ratients receiving LIFMIOR. In a double-blind, placebo-controlled, randomised chiical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent phramococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving LIFMOR were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving LIFMIOR. The clinical significance of this is unknown.

#### Autoantibody formation

Treatment with LIFMIOR may result in the formation of autoimmune antibodies (see section 4.8).

#### Haematologic reactions

Rare cases of parcy openia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with LIFMIOR. Caution should be exercised in patients being treated with LIFMIOR who have a previous history of blood dyscrasias. All patients and parents/caregivers should be acvised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on LIFMIOR, they sould seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, LIFMIOR should be discontinued.

# Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with LIFMIOR (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating LIFMIOR therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing

LIFMIOR to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

# Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of LIFMIOR and methotrexate did not result in unexpected safety findings, and the safety profile of LIFMIOR when given in combination with methotrexate was similar to the profiles reported in studies of LIFMIOR and methotrexate alone. Long-term studies to assess the safety of the combination are The use of LIFMIOR in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in pati or hepatic impairment; clinical experience in such patients is limited.

# Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using LIFMIOR in patients who have singestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, was and without identifiable precipitating factors, in patients taking LIFMIOR. There have also been are (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardi vascular disease. Some of these patients have been under 50 years of age. Two large clinical aluating the use of LIFMIOR in the treatment of CHF were terminated early du ck of efficacy. Although not conclusive, data from one of these trials suggest a possib endency toward worsening CHF in those patients assigned to LIFMIOR treatment.

# Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with LIFMIOR or placebo for moderate to severe alcoholic he tatitis, LIFMIOR was not efficacious, and the mortality rate in patients treated with LIFMIOR was significantly higher after 6 months. Consequently, LIFMIOR should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use patient who also have moderate to severe alcoholic hepatitis. caution when using LIFMIOR in

#### Wegener's granulomatosis

A placebo-controlled trial ch 89 adult patients were treated with LIFMIOR in addition to cyclophosphamide or methotrexate, and glucocorticoids) for a median standard therapy (including duration of 25 months has not shown LIFMIOR to be an effective treatment for Wegener's granulomatosis. The incrence of non-cutaneous malignancies of various types was significantly ated with LIFMIOR than in the control group. LIFMIOR is not recommended for egener's granulomatosis.

# nia in patients treated for diabetes

been reports of hypoglycaemia following initiation of LIFMIOR in patients receiving tion for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

# cial populations

In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received LIFMIOR were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

# Paediatric population

#### Vaccinations

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating LIFMIOR therapy (see Vaccinations, above).

Inflammatory bowel disease (IBD) and uveitis in patients with juvenile idiopathic arthritis (JIA) There have been reports of IBD and uveitis in JIA patients being treated with LIFMIOR (see section 4.8).

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

#### Concurrent treatment with anakinra

Adult patients treated with LIFMIOR and anakinra were observed to have a higher rate of errors infection when compared with patients treated with either LIFMIOR or anakinra alone districted data).

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with LIFMIOR and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with LIFMIOR (see sections 4.4 and 4.8). The combination LIFMIOR and anakinra has not demonstrated inc. as Id clinical benefit, and is therefore not recommended.

# Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and L FMIOR resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

#### Concurrent treatment with sulfasalazine

In a clinical study of adult patients who we're receiving established doses of sulfasalazine, to which LIFMIOR was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with LIFMIOR or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

#### Non-interactions

In clinical trials, no interactions have been observed when LIFMIOR was administered with glucocorticoids, salicy late (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrex te. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrex te, ligoxin or warfarin.

# 4.6 Febtility, pregnancy and lactation

# Wo nen of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during LIFMIOR therapy and for three weeks after discontinuation of therapy.

#### Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most

commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. LIFMIOR should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with LIFMIOR during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after he mother's last dose of LIFMIOR is generally not recommended.

# Breast-feeding

Etanercept has been reported to be excreted in human milk following subcutaneous administration. In lactating rats following subcutaneous administration, etanercept was excreted in the hilk and detected in the serum of pups. Because immunoglobulins, in common with many medicinal products, can be excreted in human milk, a decision must be made whether to discontinue theat-feeding or to discontinue LIFMIOR therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

#### **Fertility**

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

# 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to dive and use machines have been performed.

# 4.8 Undesirable effects

#### Summary of the safety profile

The most commonly reported edicate reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding) the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), allergic reactions, development of autoantibodies, itching, and fever.

Serious advers reactions have also been reported for LIFMIOR. TNF-antagonists, such as LIFMIOR, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious in ections affect fewer than 1 in 100 patients treated with LIFMIOR. Reports have included fatal and lite threatening infections and sepsis. Various malignancies have also been reported with use of LIFMIOR, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Ser ous haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with LIFMIOR use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

# Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials in adults and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ( $\geq 1/10$ );

common ( $\geq$ 1/100 to <1/10); uncommon ( $\geq$ 1/1,000 to <1/100); rare ( $\geq$ 1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10   | Common<br>≥ 1/100 to<br>< 1/10  | Uncommon<br>≥ 1/1,000 to < 1/100  | Rare<br>≥ 1/10,000 to<br>< 1/1,000   | Very Rare<br>< 1/10,000 | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|--|---|---|--|-------------------------|--|
| Infections and infestations   | Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)* |   | Serious infections<br>(including<br>pneumonia,<br>cellulitis, arthritis<br>bacterial, sepsis and<br>parasitic infection)* | Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)*   | ×                       | Hepatitis B reactivation, listeria   |
| Neoplasms<br>benign,<br>malignant and<br>unspecified<br>(including cysts<br>and polyps) |  |   | Non-melanoma skin<br>cancers* (see<br>section 4.4)  | Malignant melanoma (see section 4.4), lymphoma, leukaemia  | SI                      | Merkel cell<br>carcinoma (see<br>section 4.4)                                |
| Blood and<br>lymphatic<br>system<br>disorders   |  |   | Thrombocytopenia,<br>anaemia,<br>leukopenia,<br>neutropenia   | Pancytopenie*  | Aplastic<br>anaemia*    | Histiocytosis<br>haematophagic<br>(macrophage<br>activation<br>syndrome)*    |
| Immune system<br>disorders  |  | Allergic<br>reactions (see<br>Skin and<br>subcutaneous<br>tissue<br>disorders),<br>autoantibody<br>formation* | Vasculitis<br>(including anti-<br>neutrophilic<br>cytoplasmic an body<br>positive valcustis)                              | teriols<br>llergic/anaphylactic<br>reactions (including<br>angioedema,<br>bronchospasm),<br>sarcoidosis  |                         | Worsening of<br>symptoms of<br>dermatomyositis                               |
| Nervous system disorders  |  | 1001  |   | CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4), seizure |                         |  |
| Eye disorders<br>Cardiac<br>disorders   |  |   | Uveitis, scleritis  Worsening of cardiac failure congestive (see section 4.4)   | New onset cardiac failure congestive (see section 4.4)   |                         |  |
| Respiratory,<br>thoracic, and<br>mediastinal<br>disorders                               |  |   | SOURCE II.T)  | Interstitial lung<br>disease (including<br>pneumonitis and<br>pulmonary fibrosis)*   |                         |  |

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10   | Common ≥ 1/100 to < 1/10 | Uncommon<br>≥ 1/1,000 to < 1/100   | Rare<br>≥ 1/10,000 to<br>< 1/1,000   | Very Rare < 1/10,000             | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|--|--------------------------|--|--|----------------------------------|--|
| Hepatobiliary disorders                                       |  |                          | Elevated liver enzymes*  | Autoimmune<br>hepatitis*   |                                  |  |
| Skin and<br>subcutaneous<br>tissue disorders                  |  | Pruritus, rash           | Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash | Stevens-Johnson<br>syndrome, cutaneous<br>vasculitis (including<br>hypersensitivity<br>vasculitis), erythema<br>multiforme, lichenoid<br>reactions | Toxic<br>epidermal<br>necrolysis | ile  |
| Musculoskeletal<br>and connective<br>tissue disorders         |  |                          |  | Cutaneous lupus<br>erythematosus,<br>subacute cutaneous<br>lupus erythematosus,<br>lupus-like syndrome   | ii.                              | 30   |
| General<br>disorders and<br>administration<br>site conditions | Injection<br>site<br>reactions<br>(including<br>bleeding,<br>bruising,<br>erythema,<br>itching,<br>pain,<br>swelling)* | Pyrexia                  |  | noer   | 0                                |  |

<sup>\*</sup>see Description of selected adverse reactions, below.

# **Description of selected adverse reactions**

Malignancies and lymphoproliferative disorders

One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated inmnical trials with LIFMIOR for up to approximately **∠**IFMIOR in combination with methotrexate in the 2-year 6 years, including 231 patients treated active-controlled study. The observed rales and incidences in these clinical trials were similar to those total of 2 malignancies were reported in clinical studies of expected for the population stud ed. approximately 2 years duration olving 240 LIFMIOR-treated psoriatic arthritis patients. In clinical studies conducted for move the 2 years with 351 ankylosing spondylitis patients, 6 malignancies were d patients. In a group of 2,711 plaque psoriasis patients treated with and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma in cal cers were reported.

In a group \$7,00 patients treated with LIFMIOR in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions

Compared to placebo, patients with rheumatic diseases treated with LIFMIOR had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the LIFMIOR treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with LIFMIOR developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

#### Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with LIFMIOR for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either LIFMIOR alone, methotrexate alone or LIFMIOR in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of LIFMIOR with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with LIFMCR and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by LIFMIOR-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcul* asciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psor atil arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of LL MIOR; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fundi. Some have occurred within a few weeks after initiating treatment with LIFMIOR in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active of caronic infections) in addition to their rheumatoid arthritis (see section 4.4). LIFMIOR treatment may increase mortality in patients with established sepsis.

sociation with LIFMIOR, including invasive fungal, Opportunistic infections have been reported uding herpes zoster), bacterial (including Listeria and parasitic (including protozoal), viral (including Legionella), and atypical mycobacte jal afections. In a pooled data set of clinical trials, the overall incidence of opportunistic infection as 0.09% for the 15,402 subjects who received LIFMIOR. The ve its per 100 patient-years. In postmarketing experience, exposure-adjusted rate was Q approximately half of all ase reports of opportunistic infections worldwide were invasive fungal infections. The mocommonly reported invasive fungal infections included Candida, Pneumocystis, Aspers Ilus and Histoplasma. Invasive fungal infections accounted for more than half atients who developed opportunistic infections. The majority of the reports of the fatalities amongst were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal spergillosis (see section 4.4).

#### Autoantic oales

Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid athritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with LIFMIOR (11%) than in placebotreated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with LIFMIOR compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with LIFMIOR compared to none of placebo-treated patients). The proportion of patients treated with LIFMIOR who developed anticardiolipin antibodies was similarly increased compared to placebotreated patients. The impact of long-term treatment with LIFMIOR on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

#### Pancytopenia and aplastic anaemia

There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

#### Interstitial lung disease

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

#### Concurrent treatment with anakinra

In studies when adult patients received concurrent treatment with LIFMIOR plus a akira, a higher rate of serious infections compared to LIFMIOR alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm<sup>3</sup>). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.3).

# Elevated liver enzymes

In the double-blind periods of controlled clinical trials of etaner ep across all indications, the frequency (incidence proportion) of adverse events of elevate theer enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

#### Autoimmune hepatitis

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving an anercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled chairs trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

#### Paediatric population

Undesirable effects in pardiatric patients with juvenile idiopathic arthritis

In general, the accepte events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The type of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving LIFMIOR during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of LIFMIOR in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile

idiopathic arthritis patients receiving 3 months of LIFMIOR compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

There have been reports of inflammatory bowel disease and uveitis in JIA patients being treated with LIFMIOR from post-marketing sources, including a very small number of cases indicating a positive rechallenge (see section 4.4).

Undesirable effects in paediatric patients with plaque psoriasis

In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adve events reported were similar to those seen in previous studies in adults with plaque psoriasis.

# 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. Hearth care professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

#### 4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of Leunavoid arthritis patients. The highest dose level evaluated has been an intravenous loading dos of 32 mg/m² followed by subcutaneous doses of 16 mg/m² administered twice weekly. Ore rheumatoid arthritis patient mistakenly self-administered 62 mg LIFMIOR subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known an idote to LIFMIOR.

# 5. PHARMACOLOGICAL PROPERTIES

# 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Impuresuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (NJF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in terum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-k lodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs as a patiently in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

# Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

# Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, one study in adults with non-radiographic axial spondyloarthritis, four studies in adults with plaque psoriatis three studies in juvenile idiopathic arthritis and one study in paediatric patients with plaque psorias studies.

#### Adult patients with rheumatoid arthritis

The efficacy of LIFMIOR was assessed in a randomised, double-blind, placebo-control of study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed ben by with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Dises of 10 mg or 25 mg LIFMIOR or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage in prevenent in rheumatoid arthritis using American College of Rheumatology (ACR) response critical

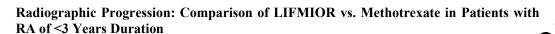
ACR 20 and 50 responses were higher in patients treated with LAFMOR at 3 and 6 months than in patients treated with placebo (ACR 20: LIFMIOR 62% and 50%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: LIFMIOR 41% and 40%, lac bo 8% and 5% at months 3 and 6, respectively; p<0.01 LIFMIOR vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

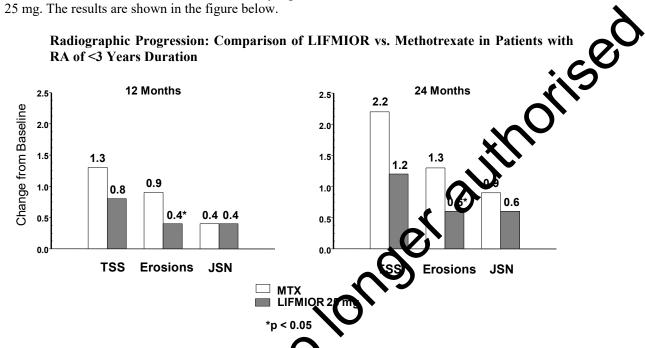
OP achieved an ACR 70 response at month 3 and Approximately 15% of subjects who received LIEM month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving LIFMIOR, the clinical responses generally opeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A q ponse was seen; results with 10 mg were intermediate between placebo and 25 mg. LIFMIOR as lignificantly better than placebo in all components of the ACR criteria, as well as other measures rheumatoid arthritis disease activity not included in the ACR response criteria, such as non stiffness. A Health Assessment Questionnaire (HAQ), which Lealth, general health status, and arthritis-associated health status included disability, vitality, r subdomains, was administered e ery 3 months during the trial. All subdomains of the HAQ were with LIFMIOR compared to controls at 3 and 6 months. improved in patients tr

After discontinuation of AFMIOR, symptoms of arthritis generally returned within a month. Re-introduction of the eatment with LIFMIOR after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received LIFMIOR without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received LIFMIOR without interruption.

the fricacy of LIFMIOR was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg LIFMIOR were administered subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, including onset of action within 2 weeks with LIFMIOR 25 mg, was similar to that seen in the previous trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with LIFMIOR 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg LIFMIOR dose had consistently less effect on structural damage than the 25 mg dose. LIFMIOR 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and LIFMIOR 25 mg. The results are shown in the figure below.





In another active-controlled, double-blind, randomised s udy, clinical efficacy, safety, and radiographic progression in RA patients treated vith DFMIOR alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median lose 20 mg), and the combination of LIFMIOR and methotrexate initiated concurrently were sineared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (midian 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheuma ic drug (DMARD) other than methotrexate.

Patients in the LIFMIOR in combina ion with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 nses and improvement for DAS and HAQ scores at both 24 and espe 52 weeks than patients in ither of the single therapy groups (results shown in table below). Significant advantage for EFMIOR in combination with methotrexate compared with LIFMIOR Medicina xate monotherapy were also observed after 24 months. monotherapy and meth

# Clinical Efficacy Results at 12 Months: Comparison of LIFMIOR vs. Methotrexate vs. LIFMIOR in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

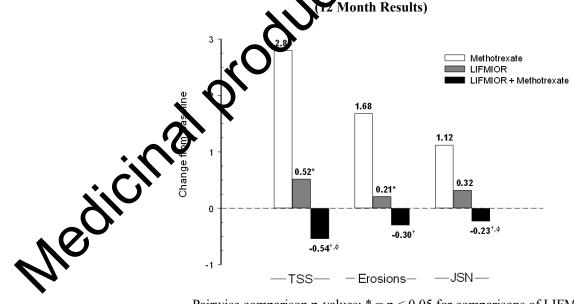
|                             | Duran        | VII       |                       |
|-----------------------------|--------------|-----------|-----------------------|
|                             |              |           | LIFMIOR +             |
| Endpoint                    | Methotrexate | LIFMIOR   | Methotrexate          |
|                             | (n = 228)    | (n = 223) | (n = 231)             |
| ACR Responses <sup>a</sup>  |              |           |                       |
| ACR 20                      | 58.8%        | 65.5%     | 74.5% <sup>†,ф</sup>  |
| ACR 50                      | 36.4%        | 43.0%     | 63.2% <sup>†,ф</sup>  |
| ACR 70                      | 16.7%        | 22.0%     | 39.8% <sup>†, φ</sup> |
| DAS                         |              |           | <b>~</b>              |
| Baseline score <sup>b</sup> | 5.5          | 5.7       | 5.5                   |
| Week 52 score <sup>b</sup>  | 3.0          | 3.0       | 2.3 <sup>†,‡</sup>    |
| Remission <sup>c</sup>      | 14%          | 18%       | 37% <sup>†, φ</sup>   |
| HAQ                         |              |           |                       |
| Baseline                    | 1.7          | 1.7       | <b>7 6</b> .8         |
| Week 52                     | 1.1          | 1.0       | 0.8 <sup>†, φ</sup>   |

a: Patients who did not complete 12 months in the study were considered to be non-responders.

Pairwise comparison p-values:  $\dagger = p < 0.05$  for comparisons of LIFMLOR + methotrexate vs. methotrexate and  $\phi = p < 0.05$  for comparisons of LIFMLOR + itemotrexate vs. LIFMLOR.

Radiographic progression at 12 months was significantly less in the LIFMIOR group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

Radiographic Progression: Comparis in of LIFMIOR vs. Methotrexate vs. LIFMIOR in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration



Pairwise comparison p-values: \* = p < 0.05 for comparisons of LIFMIOR vs. methotrexate, † = p < 0.05 for comparisons of LIFMIOR + methotrexate vs. methotrexate and  $\varphi$  = p < 0.05 for comparisons of LIFMIOR + methotrexate vs. LIFMIOR.

b: Values for Disease Activity Score (DAS) are means.

c: Remission is defined as DAS < 1.6.

Significant advantages for LIFMIOR in combination with methotrexate compared with LIFMIOR monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for LIFMIOR monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change  $\leq$  0.5) at 24 months was higher in the LIFMIOR in combination with methotrexate group compared with the LIFMIOR alone and methotrexate alone groups (62%, 50%, and 36%, respectively; p<0.05). The difference between LIFMIOR alone and methotrexate alone was also significant (p<0.05). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg LIFMIOR (two 25 mg SC injections) administered once wee dy were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA In his study, 53 patients received placebo, 214 patients received 50 mg LIFMIOR once weekly and 153 patients received 25 mg LIFMIOR twice weekly. The safety and efficacy profiles of the two LIFMIOR treatment regimens were comparable at week 8 in their effect on signs and winptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens.

# Adult patients with psoriatic arthritis

Medicinal

The efficacy of LIFMIOR was assessed in a randomised, double-bline o-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years. rs of age and had active psoriatic arthritis ( $\geq 3$  swollen joints and  $\geq 3$  tender joints) in at least of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticula writis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asylum etric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psorbsis with a qualifying target lesion  $\geq 2$  cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on meth therapy (stable for  $\geq 2$  months) could continue at a stable dose of  $\leq 25$  mg/week method rexate. Doses of 25 mg of LIFMIOR (based on dose-finding studies in patients with rheun toid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the do ofe-band study, patients could enter a long-term open-label extension study for a total duration of

Clinical responses were express d at percentages of patients achieving the ACR 20, 50, and 70 response and percentages with Exprovement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table selov.

# Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

| Control                      | icu i i iai |                      |              |
|------------------------------|-------------|----------------------|--------------|
|                              | Percent     | of Patients          |              |
|                              | Placebo     | LIFMIOR <sup>a</sup> |              |
| Psoriatic Arthritis Response | n = 104     | n = 101              |              |
| ACR 20                       |             |                      | •            |
| Month 3                      | 15          | 59 <sup>b</sup>      | $\sim$       |
| Month 6                      | 13          | 50 <sup>b</sup>      |              |
| ACR 50                       |             |                      | . 60         |
| Month 3                      | 4           | $38^{b}$             |              |
| Month 6                      | 4           | 37 <sup>b</sup>      |              |
| ACR 70                       |             |                      |              |
| Month 3                      | 0           | 11 <sup>b</sup>      | <b>X '</b> ' |
| Month 6                      | 1           | 9°                   |              |
| PsARC                        |             | <i>─</i>             |              |
| Month 3                      | 31          | <b>16</b> p          |              |
| Month 6                      | 23          |                      |              |
| a: 25 mg LIFMIOR SC twice w  | eekly       | V                    |              |

a: 25 mg LIFMIOR SC twice weekly b: p < 0.001, LIFMIOR vs. placebo

c: p < 0.01, LIFMIOR vs. placebo

Among patients with psoriatic arthritis who received LIFMLOR, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained brough 6 months of therapy. LIFMIOR was significantly better than placebo in all measures or lisease activity (p < 0.001), and responses were similar with and without concomitant methods, at therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index score was significantly improved at all time toints in psoriatic arthritis patients treated with LIFMIOR, relative to placebo (p < 0.001).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in the table below. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change  $\leq$  0.5) at 12 months was higher in the LIFMIOR group compared with the placebo group (73% vs. 47%, respectively, p  $\leq$  0.00%). The effect of LIFMIOR on radiographic progression was maintained in patients who considued on treatment during the second year. The slowing of peripheral joint damage was observed in attents with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

| VO.      | Placebo     | Etanercept                |
|----------|-------------|---------------------------|
| Time     | (n = 104)   | (n = 101)                 |
| Month 12 | 1.00 (0.29) | -0.03 (0.09) <sup>a</sup> |

SE = standard error.

a. p = 0.0001.

LIFMIOR treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of LIFMIOR in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.

No study has been performed in patients with psoriatic arthritis using the 50 mg once-weekly dosing regimen. Evidence of efficacy for the once-weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

Adult patients with ankylosing spondylitis

The efficacy of LIFMIOR in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice-weekly administration of 25 mg LIFMIOR with placebo. A total of 401 patients were enrolled, from which 203 were treated with LIFMIOR. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient \$\displace\$ global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of LIFMIOR (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥20% improvement in at least 3 if the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining or main. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70° Chaprovement, respectively.

Compared to placebo, treatment with LIFMIOR resulted in significant provements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of herapy.

| Responses of Patients with Ankylosing Spondylitis in a<br>Placebo-cont old Trial |            |                 |  |  |  |  |
|--|------------|-----------------|--|--|--|--|
| .1   | Percent of | of Patients     |  |  |  |  |
| Ankylosing Spondylitis   | Placebo    | LIFMIOR         |  |  |  |  |
| Response   | N = 139    | N = 138         |  |  |  |  |
| ASAS 20  |            |                 |  |  |  |  |
| 2 weeks  | 22         | 46 <sup>a</sup> |  |  |  |  |
| 3 months   | 27         | 60 <sup>a</sup> |  |  |  |  |
| 6 months   | 23         | 58ª             |  |  |  |  |
| ASAS 50  |            |                 |  |  |  |  |
| 2 w eks  | 7          | 24 <sup>a</sup> |  |  |  |  |
| 3 n onths  | 13         | 45 <sup>a</sup> |  |  |  |  |
| 6 nonths   | 10         | 42ª             |  |  |  |  |
| ASAS 70  |            |                 |  |  |  |  |
| 2 weeks  | 2          | 12 <sup>b</sup> |  |  |  |  |
| 3 months   | 7          | 29 <sup>b</sup> |  |  |  |  |
| 6 months   | 5          | 28 <sup>b</sup> |  |  |  |  |
| a: p<0.001, LIFMIOR vs. pl   | acebo      | 1               |  |  |  |  |
| b: $p = 0.002$ , LIFMIOR vs. 1   | placebo    |                 |  |  |  |  |

2 12<sup>b</sup>
6 months 7 29<sup>b</sup>
a: p<0.001, LIFMIOR vs. placebo
b: p = 0.002, LIFMIOR vs. placebo

Among patients with ankylosing spondylitis who received LIFMIOR, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg LIFMIOR (two 25 mg SC injections) administered once weekly vs. 25 mg LIFMIOR administered twice weekly were evaluated in a double-blind,

placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once-weekly and 25 mg twice-weekly regimens were similar.

Adult patients with non-radiographic axial spondyloarthritis

The efficacy of LIFMIOR in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received LIFMIOR 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. The double-blind period was followed by an open-label period during which all patients receive LIFMIOR 50 mg weekly for up to an additional 92 weeks. MRIs of the sacrein action and spine were obtained to assess inflammation at baseline and at weeks 12 and 104.

Compared to placebo, treatment with LIFMIOR resulted in statistically significant in provement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed to the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent in attents Achieving

**Endpoints** 

| apoints                |             |                   |
|------------------------|-------------|-------------------|
| Double-Blind Clinical  | Placebo     | LIFMIOR           |
| Responses at Week 12   | N=106 to 09 | N=103 to 105*     |
| ASAS** 40              | 1/2         | 32.4 <sup>b</sup> |
| ASAS 20                | 36          | 52.4°             |
| ASAS 5/6               | 10.4        | $33.0^{a}$        |
| ASAS partial remission | 11.9        | 24.8°             |
| BASDAI***50            | 23.9        | 43.8 <sup>b</sup> |

<sup>\*</sup>Some patients did not provide complete data for each endpoint

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Carada score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving LIFMIOR. Adjusted mean change from baseline was 3.8 for LIFMIOR treated (n=95) versus 0.8 for placeboare tell (n=105) patients (p<0.001). At week 104, the mean change from baseline in the SPARCC score measured on MRI for all LIFMIOR-treated subjects was 4.64 for the SIJ (n=153) and 1.00 the spine (n=154).

LIFMIOR shows a statistically significantly greater improvement from baseline to week 12 compared to place to in most health-related quality of life and physical function assessments, including BASFI (Batl Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 Physical Component Score.

first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the modified New York Radiological Grade, indicative of axial spondyloarthropathy.

<sup>\*\*</sup>ASAS=Assessments in Spondylom britis International Society

<sup>\*\*\*</sup>Bath Ankylosing Spondylitis Disesse Activity Index

a: p<0.001, b:<0.01 and c:<0.05, respectively between LIFMIOR and placebo

Adult patients with plaque psoriasis

LIFMIOR is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the three major systemic therapies as available.

The efficacy of LIFMIOR versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing LIFMIOR with other systemic therapies. Instead, the safety and efficacy of LIFMIOR were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis (volving  $\geq$  10% of the body surface area who were  $\geq$  18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of LIFMIOR (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PAST) to 0 at screening. LIFMIOR was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double clind treatment period, patients received placebo or one of the above three LIFMIOR dose. After 12 weeks of treatment, patients in the placebo group began treatment with blinded LIFMOR (25 mg twice a week); patients in the active treatment groups continued to week 24 on the cose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same increasion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg LIFMIOR, & placebo twice a week for 12 weeks and then all patients received open-label 25 mg LIFMIOR twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had smiller inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg KFNIO cor placebo once weekly for 12 weeks and then all patients received open-label 50 mg LIFNIO conce weekly for an additional 12 weeks.

In study 1, the LIFMIOR-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) (p<0.0001). At 24 weeks, 56% of patients in the LIFMIOR-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

# Responses of Patients with Psoriasis in Studies 2, 3 and 4

|                     | Study 2 |     |                 |       |                 |         | Study 3 |         |         | Study 4      |                    |  |
|---------------------|---------|-----|-----------------|-------|-----------------|---------|---------|---------|---------|--------------|--------------------|--|
|                     |         |     | LIFN            | /IOR- |                 |         | LIFMIOR |         |         | LIFN         | MIOR               |  |
|                     |         | 25  | mg              | 50    | mg              |         | 25 mg   | 50 mg   |         | 50 mg        | 50 mg              |  |
|                     | Placebo | BI  | W               | BI    | W               | Placebo | BIW     | BIW     | Placebo | QW           | QW                 |  |
|                     | n = 166 | n=  | n =             | n =   | n =             | n = 193 | n = 196 | n = 196 | n = 46  | n = 96       | n = 90             |  |
|                     | wk 12   | 162 | 162             | 164   | 164             | wk 12        | wk 24 <sup>a</sup> |  |
| Respons             |         | wk  | wk              | wk    | wk              |         |         |         |         |              |                    |  |
| e (%)               |         | 12  | 24 <sup>a</sup> | 12    | 24 <sup>a</sup> |         |         |         |         |              |                    |  |
| PASI 50             | 14      | 58* | 70              | 74*   | 77              | 9       | 64*     | 77*     | 9       | 69*          | 83                 |  |
| PASI 75             | 4       | 34* | 44              | 49*   | 59              | 3       | 34*     | 49*     | 2       | 38*          | 71                 |  |
| DSGA <sup>b</sup> , |         |     |                 |       |                 |         |         |         |         |              | 11                 |  |
| clear or            |         |     |                 |       |                 |         |         |         |         | (            | <b>7</b> ,         |  |
| almost              |         |     |                 |       |                 |         |         |         |         |              |                    |  |
| clear               | 5       | 34* | 39              | 49*   | 55              | 4       | 39*     | 57*     | 4       | <b>X</b> 33* | 64                 |  |

<sup>\*</sup> $p \le 0.0001$  compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving LIFMIOR 25 mg BIW or 50 mg once weekly from week 13 to week 24. b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received LIFMIOR, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and we enquitained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patent. Who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned, with median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related strious adverse events were observed. There was some evidence to support a benefit of re-take nent with LIFMIOR in patients initially responding to treatment.

In study 3, the majority of patients (7,22) who were initially randomised to 50 mg twice weekly and had their LIFMIOR dose decreased it week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the LYFMION freated group had a higher proportion of patients with PASI 75 at week 12 (38%) compare 1 to the placebo-treated group (2%) (p<0.0001). For patients who received 50 mg once weekly through the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where LIFMIOR was given without interruption, Winking responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

# Antibodies to LIFMIOR

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

# Paediatric population

Paediatric patients with juvenile idiopathic arthritis

The safety and efficacy of LIFMIOR were assessed in a two-part study in 69 chi polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 years with moderately to severely active polyarticular-course juvenile idiopathic arthritis refractor intolerant of, methotrexate were enrolled; patients remained on a stable dose of a six anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 ng m ximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) LIFMIOR subcrita. twice weekly. In part 2, patients with a clinical response at day 90 were randomised ain on LIFMIOR or receive placebo for four months and assessed for disease flare. Response ere theasured using the ACR Pedi 30), defined as  $\geq 30\%$  improvement in at least three of six and  $\geq 30\%$  worsening in no more than one of six JRA core set criteria, including active joint count, lightation of motion, physician and patient/parent global assessments, functional assessment, and egyth te sedimentation rate (ESR). Disease flare was defined as a  $\geq 30\%$  worsening in three of sh JRA core set criteria and  $\geq 30\%$  improvement in not more than one of the six JRA core set crite a and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients reneating on LIFMIOR experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was ≥ 116 days for patients who could LIFMIOR and 28 days for patients who received placebo. Of patients who demonstrated actinical response at 90 days and entered part 2 of the study, some of the patients remaining on LIFMIOR continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-lab 1, salety extension study, 58 paediatric patients from the above study (from the age of 4 years at time (f incollment) continued to receive LIFMIOR for up to 10 years. Rates of serious adverse elepts and serious infections did not increase with long-term exposure.

Long tern safety of LIFMIOR monotherapy (n=103), LIFMIOR plus methotrexate (n=294), or a still trexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 yersus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study, 60 patients with extended oligoarthritis (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with LIFMIOR at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued LIFMIOR therapy in patients who do not respond within 3 months of initiating LIFMIOR therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of LIFMIOR following its long-term use in patients with JIA.

# Paediatric patients with plaque psoriasis

The efficacy of LIFMIOR was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by an sPGA score  $\geq$  3, involving  $\geq$  10% of the BSA, and PASI  $\geq$  12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received LIFMIOR 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to LIFMIOR had positive efficacy responses (e.g., PASI 73) than those randomised to placebo.

# Paediatric Plaque Psoriasis Outcomes at 12 Weeks

|                                  | LIFMIOR<br>0.8 mg/kg Once | <b>1</b> 0          |
|----------------------------------|---------------------------|---------------------|
|                                  | Weekly                    | Placebo             |
| PASI 75, n (%)                   | $(N = 106)$ $60 (57\%)^a$ | N = 105<br>12 (11%) |
| PASI 50, n (%)                   | 79 (75%) <sup>a</sup>     | 24 (23%)            |
| sPGA "clear" or "minimal", n (%) | 56 (53%) <sup>a</sup>     | 14 (13%)            |

Abbreviation: sPGA-static Physician Global Assessment

After the 12-week double-blind treatment period, all patients received LIFMIOR 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind, criod.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (los ONPASI 75 response) compared with patients re-randomised to LIFMIOR. With continued the appression were maintained up to 48 weeks.

The long-term safety and effectiveness of LIFMIOR 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-lated extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with LIFMIOR was generally comparable to the original 48-week study and did not reveal any new safety findings.

# 5.2 Pharmacokinetic properties

Etan ree t serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) ethod, which may detect ELISA-reactive degradation products, as well as the parent compound.

#### Absorption 4 4 1

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg LIFMIOR, the average maximum serum concentration observed in healthy volunteers was  $1.65 \pm 0.66 \,\mu\text{g/ml}$ , and the area under the curve was  $235 \pm 96.6 \,\mu\text{g} \cdot \text{hr/ml}$ .

Mean serum concentration profiles at steady state in treated RA patients were  $C_{max}$  of 2.4 mg/l vs. 2.6 mg/l,  $C_{min}$  of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg

a. p < 0.0001 compared with placebo

LIFMIOR once weekly (n=21) vs. 25 mg LIFMIOR twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466  $\mu$ g•hr/ml and 474  $\mu$ g•hr/ml for 50 mg LIFMIOR once weekly (N=154) and 25 mg twice weekly (N=148), respectively.

#### Distribution

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4.

# **Elimination**

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of LIFMIC2 in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are visible.

There is no apparent pharmacokinetic difference between males and female

# Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

# Special populations

# Renal impairment

Although there is elimination of radioactivity in print after administration of radiolabelled etanercept to patients and volunteers, increased etanercept one ntrations were not observed in patients with acute renal failure. The presence of renal in pairment should not require a change in dosage.

# Hepatic impairment

Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment mode not require a change in dosage.

# Elderly

The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Cle rance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

#### Paediatric popu at on

# Paedictrix putients with juvenile idiopathic arthritis

In a foly ricular-course juvenile idiopathic arthritis trial with LIFMIOR, 69 patients (aged 4 to 5 v ars) were administered 0.4 mg LIFMIOR/kg twice weekly for three months. Serum concentration probles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

#### Paediatric patients with plaque psoriasis

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed

in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly.

# 5.3 Preclinical safety data

In the toxicological studies with LIFMIOR, no dose-limiting or target organ toxicity was evident. LIFMIOR was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with LIFMIOR due to the development of neutralising antibodies in rodents.

LIFMIOR did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. LIFMIOR did not envious dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-to see cerum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

# 6. PHARMACEUTICAL PARTICULARS

# 6.1 List of excipients

Powder Mannitol (E421) Sucrose Trometamol

Solvent

Water for injections

# 6.2 Incompatibilities

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

# 6.3 Shelf life

4 years.

Chemical and physical in-use stability has been demonstrated for 6 hours at temperatures of up to 25°C after reconstitution. From a microbiological point of view, the reconstituted medicinal product should be used immediately. If not used immediately, storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 6 hours at temperatures of up to 25°C unless reconstitution has taken place in controlled and validated aseptic conditions.

# 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

LIFMIOR may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks of removal from refrigeration.

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

# 6.5 Nature and contents of container

Clear glass vial (4 ml, type I glass) with rubber stoppers, aluminium seals, and flip-off plastic caps. LIFMIOR is supplied with pre-filled syringes containing water for injection. The syringes are type I glass. Cartons contain 4, 8 or 24 vials of LIFMIOR with 4, 8 or 24 pre-filled solvent syringes, 4, 8 or 24 needles, 4, 8 or 24 vial adaptors and 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

# 6.6 Special precautions for disposal and other handling

# Instructions for use and handling

LIFMIOR is reconstituted with 1 ml water for injections before use, and administered by subcutaneous injection. LIFMIOR contains no antibacterial preservative, and therefore solutions prepared with water for injections should be administered as soon as possible and within 6 hours following reconstitution. The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flake or particles. Some white foam may remain in the vial – this is normal. LIFMIOR should not be used if all the powder in the vial is not dissolved within 10 minutes. If this is the case, start again with another vial.

Comprehensive instructions for the preparation and administration of the reconstrated LIFMIOR vial are given in the package leaflet, section 7, "INSTRUCTIONS FOR PREPARATION AND GIVING AN INJECTION OF LIFMIOR".

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

# 7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium

#### 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1165/002 EU/1/16/1165/003 EU/1/16/1165/004

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

Date of first authorisation: 13 February 2017 Date of hist enewal: {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 <a href="http://www.ema.europa.eu">http://www.ema.europa.eu</a>.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

# 1. NAME OF THE MEDICINAL PRODUCT

LIFMIOR 25 mg solution for injection in pre-filled syringe. LIFMIOR 50 mg solution for injection in pre-filled syringe.

# 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

25 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 25 mg of etanercept.

50 mg solution for injection in pre-filled syringe Each pre-filled syringe contains 50 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression, system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extra exclur ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH<sub>2</sub> and CH<sub>3</sub> regions, but not the CN region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is 1.7 x 10<sup>6</sup> units/mg.

Jihorised

For the full list of excipients, see section 6.1.

# 3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, and colour ess to pale yellow or pale brown.

#### 4 CLINICAL PARTICULARS

# 4.1 Therapeutic indications

#### Rheumatoid art irius

LIFMIQIS in combination with methotrexate is indicated for the treatment of moderate to severe active rheuractors arthritis in adults when the response to disease-modifying antirheumatic drugs, including method are (unless contraindicated), has been inadequate.

LIFMIOR can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

LIFMIOR is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

LIFMIOR, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

# Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

LIFMIOR has not been studied in children aged less than 2 years.

# Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. LIFMIOR has been hown 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 symmetric subtypes of the disease.

# Axial spondyloarthritis

# Ankylosing spondylitis (AS)

Treatment of adults with severe active ankylosing spondylitis who have bad an inadequate response to conventional therapy.

# Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axian pondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

# Plaque psoriasis

Treatment of adults with moderate it severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (NUVA) (see section 5.1).

#### Paediatric plaque psoriasis

Treatment of chronic eve e plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

# 4.2 Posology and method of administration

LIFMION to atment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, k Vosing spondylitis, non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patients treated with LIFMIOR should be given the Patient Alert Card.

LIFMIOR is available in strengths of 10, 25 and 50 mg.

#### **Posology**

#### Rheumatoid arthritis

25 mg LIFMIOR administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. The recommended dose is 25 mg LIFMIOR administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

# Plaque psoriasis

The recommended dose of LIFMIOR is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with LIFMIOR should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with LIFMIOR is indicated, the same will lance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 ctg size weekly.

# Special populations

Renal and hepatic impairment
No dose adjustment is required.

#### Elderly

No dose adjustment is required. Posology and administration are the same as for adults 18-64 years of age.

# Paediatric population

The dosage of LIFMIOR is based on body weight to paediatric patients. Patients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using the powder and solvent for solution for injection presentations or the powder for solution for injection presentations (see below for dosing for specific indications). Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.

# Juvenile idiopathic arthritis

The recommended dose is 0.4 my/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given on the weekly. Discontinuation of treatment should be considered in patients who show no response of cr 4 months.

The 10 mg vial at high may be more appropriate for administration to children with JIA below the weight of 70 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety land from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to have seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of LIFMIOR in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age 6 years and above)

The recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with LIFMIOR is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of LIFMIOR in children aged below 6 years in the indication plaque psoriasis.

# Method of administration

LIFMIOR is administered by subcutaneous injection (see section 6.6).

noiisel Comprehensive instructions for administration are given in the package leaflet, section 7, "Instructions for preparation and giving an injection of LIFMIOR".

#### 4.3 **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Sepsis or risk of sepsis.

Treatment with LIFMIOR should not be initiated in patients with active infection, i cluding chronic or localised infections.

# Special warnings and precautions for use

In order to improve the traceability of biological medicinal prod ademark and the batch number of the administered product should be clearly recor stated) in the patient file.

#### Infections

Patients should be evaluated for infections before, dans g, and after treatment with LIFMIOR, taking into consideration that the mean elimination half tanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, a ortunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of LIFMIOR (see section 4.8). These infections were due to bacert, micobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatm sometimes death. In evaluating patients for infections, the nistic infections (e.g., exposure to endemic mycoses) should be patient's risk for relevant ort considered.

w infection while undergoing treatment with LIFMIOR should be monitored ion of LIFMIOR should be discontinued if a patient develops a serious infection. The safety ff cacy of LIFMIOR in patients with chronic infections have not been evaluated. Physician should exercise caution when considering the use of LIFMIOR in patients with a history of hronic infections or with underlying conditions that may predispose patients to such as advanced or poorly controlled diabetes.

ses of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary ocation, have been reported in patients treated with LIFMIOR.

Before starting treatment with LIFMIOR, 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, i.e., tuberculin skin test and chest X-ray, 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's alert 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, LIFMIOR therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of LIFMIOR, and in accordance with local recommendations. In this situation, the benefit/risk balance of LIFMIOR therapy should be very carefully considered.

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 LIFMIOR treatment.

# Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including LIFMIOR, has been reported. This factudes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg registive. Patients should be tested for HBV infection before initiating treatment with LIFMIOR. For patients who test positive for HBV infection, consultation with a physician with expertise in the reatment of hepatitis B is recommended. Caution should be exercised when administering LIFMIOR in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in an unction with TNF-antagonist therapy are not available. In patients who develop I BV infection, LIFMIOR should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

# Worsening of hepatitis C

There have been reports of worsening of hepatitis C in path ats receiving LIFMIOR. LIFMIOR should be used with caution in patients with a history of her art is C.

#### Concurrent treatment with anakinra

Concurrent administration of LIFMIOR and tanakhara has been associated with an increased risk of serious infections and neutropenia compared LIFMIOR alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of LIFMIOR and anakinra is not recommended (see sections 4.5 and 4.8).

#### Concurrent treatment with about

In clinical studies, concurrent administration of abatacept and LIFMIOR resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

#### Allergic reaction

The needle cover of the pre-filled syringe contains latex (dry natural rubber) that may cause hypersens tivity reactions when handled by, or when LIFMIOR is administered to, persons with known of possible latex sensitivity.

We git reactions associated with LIFMIOR administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, LIFMIOR therapy should be discontinued immediately and appropriate therapy initiated.

# <u>Immunosuppression</u>

The possibility exists for TNF-antagonists, including LIFMIOR, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with LIFMIOR, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue LIFMIOR therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of LIFMIOR in patients with immunosuppression have not been evaluated.

# Malignancies and lymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. 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.

Based on current knowledge, a possible risk for the development of lym to has, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF antigonist cannot be excluded. Caution should be exercised when considering TNF-antagonist the apy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy  $\leq$  18 years of age), including LIFMIOR, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

#### Skin cancers

Melanoma and non-melanoma s'an carcer (NMSC) have been reported in patients treated with TNF-antagonists, including LECA. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with LIFMIOR. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed in patients receiving LIFMOR compared with control patients, particularly in patients with psoriasis.

#### Vaccinations

Live vaccines should not be given concurrently with LIFMIOR. No data are available on the secondary transmission of infection by live vaccines in patients receiving LIFMIOR. In a coulde-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving LIFMIOR were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patients not receiving LIFMIOR. The clinical significance of this is unknown.

# **Autoantibody formation**

Treatment with LIFMIOR may result in the formation of autoimmune antibodies (see section 4.8).

# Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with LIFMIOR. Caution should be exercised in patients being treated with LIFMIOR who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on LIFMIOR, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, LIFMIOR should be discontinued.

# Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with LIFMIOR (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating LIFMIOR therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing LIFMIOR to patients with pre-existing or recent onset of demyelinating disease, and be seen who are considered to have an increased risk of developing demyelinating disease.

# Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis, at ents, the combination of LIFMIOR and methotrexate did not result in unexpected safety findings and the safety profile of LIFMIOR when given in combination with methotrexate was significantly by profiles reported in studies of LIFMIOR and methotrexate alone. Long-term studies to access the safety of the combination are ongoing. The long-term safety of LIFMIOR in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of LIFMIOR in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

# Renal and hepatic impairment

Based on pharmacokinetic data (see section .2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

# Congestive heart failure (Cardin Colure congestive)

Physicians should use caution when using LIFMIOR in patients who have congestive heart failure (CHF). There have been pertmarketing reports of worsening of CHF, with and without identifiable precipitating factors, it patients taking LIFMIOR. There have also been rare (< 0.1%) reports of new onset CHF, including CAF in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. Two large clinical trials evaluating the use of LIFMIOR in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to LIFMIOR treatment.

#### Scorolic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised patients treated with LIFMIOR or placebo for moderate to severe alcoholic hepatitis, LIFMIOR was not efficacious, and the mortality rate in patients treated with LIFMIOR was significantly higher after 6 months. Consequently, LIFMIOR should not be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using LIFMIOR in patients who also have moderate to severe alcoholic hepatitis.

#### Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with LIFMIOR in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown LIFMIOR to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly

higher in patients treated with LIFMIOR than in the control group. LIFMIOR is not recommended for the treatment of Wegener's granulomatosis.

#### Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of LIFMIOR in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

#### Special populations

In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or other who received LIFMIOR were observed compared with volume and the serious infections in patients age 65 or other who received LIFMIOR were observed compared with volume and the serious infections in patients age 65 or other who received LIFMIOR were observed compared with volume and the serious infections in patients age 65 or other whose serious adverse events, and serious infections in patients age 65 or other whose serious infections in patients age exercised when treating the elderly and particular attention paid with respect to occurren infections.

#### Paediatric population

#### Vaccinations

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating LIF Vaccinations, above).

Inflammatory bowel disease (IBD) and uveitis in patients with i opathic arthritis (JIA) There have been reports of IBD and uveitis in JIA patients by reated with LIFMIOR (see section 4.8).

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

#### Concurrent treatment with anakinra

Adult patients treated with LIFMIOR and a akinra were observed to have a higher rate of serious infection when compared with patients t with either LIFMIOR or anakinra alone (historical data).

In addition, in a double-blind, place ontrolled trial in adult patients receiving background FMIOR and anakinra were observed to have a higher rate of methotrexate, patients treated serious infections (7%) and openia than patients treated with LIFMIOR (see sections 4.4 and AIOR and anakinra has not demonstrated increased clinical benefit, and is 4.8). The combination L therefore not recommende

#### with abatacept

s concurrent administration of abatacept and LIFMIOR resulted in increased erious adverse events. This combination has not demonstrated increased clinical use is not recommended (see section 4.4).

#### rent treatment with sulfasalazine

Elinical study of adult patients who were receiving established doses of sulfasalazine, to which FMIOR was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with LIFMIOR or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

#### Non-interactions

In clinical trials, no interactions have been observed when LIFMIOR was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin.

#### 4.6 Fertility, pregnancy and lactation

#### Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during LIFMIOR therapy and for three weeks after discontinuation of therapy.

#### Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm toxing foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have b investigated in two observational cohort studies. A higher rate of major birth defects was observational one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with thos commonly reported in the general population and no particular pattern of abnormalities identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations another observational multi-country registry study comparing the risk of adverse regnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=436) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of m irth defects (crude odds 6 after adjusting for ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.2 country, maternal disease, parity, maternal age and smoking in early premancy). This study also showed no increased risks of minor birth defects, preterm birth, an or infections in the first year of life for infants born to women exposed to etanercept durin gnancy. LIFMIOR should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with LIFMIOR during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of LIFMIOR is generally not recommended.

#### Breast-feeding

Etanercept has been reported to be excreted in human milk following subcutaneous administration. In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Because in a hogolobulins, in common with many medicinal products, can be excreted in human milk, a dicisi in must be made whether to discontinue breast-feeding or to discontinue LIFMIOR therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for he yoman.

#### Fertility

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

#### 497. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

#### 4.8 Undesirable effects

#### Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for LIFMIOR. TNF-antagonists, such as LIFMIOR, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with LIFMIOR. Reports have included fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of LIFMIOR, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with LIFMIOR use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

#### <u>Tabulated list of adverse reactions</u>

The following list of adverse reactions is based on experience from clinical trials in adults and postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ( $\geq 1/100$ ); common ( $\geq 1/100$ ); uncommon ( $\geq 1/1,000$ ); rare ( $\geq 1/10,000$ ); very rare ( $\leq 1/10,000$ ); not known (cannot be estimated from the available data).

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10   | Common ≥ 1/100 to < 1/10  | Uncommon<br>≥ 1/1,000 to < 1/100  | Rare ≥ 1/10,000 to < 1/1,000  | Very Rare<br>< 1/10,000 | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|--|---|---|---|-------------------------|--|
| Infections and infestations   | Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)* |   | Serious infections<br>(including<br>pneumonia,<br>cellulitis, arthritis<br>bacterial, serious<br>parasitic of fection)* | ube culosis, op, atunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)* |                         | Hepatitis B<br>reactivation,<br>listeria                                     |
| Neoplasms<br>benign,<br>malignant and<br>unspecified<br>(including cysts<br>and polyps) |  | ,001  | on-melanoma skin<br>cancers* (see<br>section 4.4)   | Malignant melanoma<br>(see section 4.4),<br>lymphoma,<br>leukaemia  |                         | Merkel cell<br>carcinoma (see<br>section 4.4)                                |
| Blood and<br>lymphatic<br>system disorders  | 9/   | <b>)</b>  | Thrombocytopenia,<br>anaemia,<br>leukopenia,<br>neutropenia   | Pancytopenia*   | Aplastic<br>anaemia*    | Histiocytosis<br>haematophagic<br>(macrophage<br>activation<br>syndrome)*    |
| Immune system<br>disorders  |  | Allergic<br>reactions (see<br>Skin and<br>subcutaneous<br>tissue<br>disorders),<br>autoantibody<br>formation* | Vasculitis<br>(including anti-<br>neutrophilic<br>cytoplasmic antibody<br>positive vasculitis)                          | Serious<br>allergic/anaphylactic<br>reactions (including<br>angioedema,<br>bronchospasm),<br>sarcoidosis  |                         | Worsening of<br>symptoms of<br>dermatomyositis                               |

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10  | Common<br>≥ 1/100 to<br>< 1/10 | Uncommon<br>≥ 1/1,000 to < 1/100   | Rare<br>≥ 1/10,000 to<br>< 1/1,000   | Very Rare<br>< 1/10,000          | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|---|--------------------------------|--|--|----------------------------------|--|
| Nervous system<br>disorders                                   |   |                                |  | CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy (see section 4.4) see tree | ali                              | noile  |
| Eye disorders   |   |                                | Uveitis, scleritis   | section 1.17   |                                  |  |
| Cardiac   |   |                                | Worsening of   | New cas t cardia.  |                                  |  |
| disorders   |   |                                | cardiac failure congestive (see section 4.4)   | failun congestive<br>see section 4.4)  |                                  |  |
| Respiratory,<br>thoracic, and<br>mediastinal<br>disorders     |   |                                | 20   | disease (including<br>pneumonitis and<br>pulmonary fibrosis)*  |                                  |  |
| Hepatobiliary   |   |                                | Elevated liver   | Autoimmune   |                                  |  |
| disorders   |   |                                | enzy, nes*   | hepatitis*   | m ·                              |  |
| Skin and subcutaneous tissue disorders                        |   | Pruritus, rash                 | Ingioce ma, prorisis (including ew onset or vorsening and pustular, primarily palms and soles), urticaria, psoriasiform rash | Stevens-Johnson<br>syndrome, cutaneous<br>vasculitis (including<br>hypersensitivity<br>vasculitis), erythema<br>multiforme, lichenoid<br>reactions   | Toxic<br>epidermal<br>necrolysis |  |
| Musculoskeletal<br>and connective<br>tissue disorders         | 7   | ),                             |  | Cutaneous lupus<br>erythematosus,<br>subacute cutaneous<br>lupus erythematosus,<br>lupus-like syndrome   |                                  |  |
| General<br>disorders and<br>administration<br>site conditions | reactions<br>(including<br>bleeding,<br>bruising,<br>erythema,<br>itching,<br>pain, | Pyrexia                        |  | iupus-nae syndionie  |                                  |  |

\*see Description of selected adverse reactions, below.

## Description of selected adverse reactions

Malignancies and lymphoproliferative disorders

One hundred and twenty-nine (129) new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with LIFMIOR for up to approximately 6 years,

including 231 patients treated with LIFMIOR in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 LIFMIOR-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in LIFMIOR-treated patients. In a group of 2,711 plaque psoriasis patients treated with LIFMIOR in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with LIFMIOR in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also be a received in the postmarketing period (see section 4.4).

#### *Injection site reactions*

Compared to placebo, patients with rheumatic diseases treated with LIFMIOR had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions and by occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the LIFMIOR treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, applications and by 13.6% of patients treated with LIFMIOR developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

#### Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or wics) was observed. Serious infections occurred in 6.3% requiring hospitalisation or intravenous th IFMIOR for up to 48 months. These included abscess (at of rheumatoid arthritis patients treated w various sites), bacteraemia, bronchitis, barsitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroente hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonit monia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary traction, vasculitis, and wound infection. In the 2-year active-controlled study wh re patients were treated with either LIFMIOR alone, methotrexate alone or with methotrexate, the rates of serious infections were similar among the LIFMIOR in combination er, it cannot be excluded that the combination of LIFMIOR with e associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with LIFMIOR and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Sericus il fections experienced by LIFMIOR-treated patients included cellulitis, gastroenteritis, beet nonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of LIFMIOR; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with LIFMIOR in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). LIFMIOR treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with LIFMIOR, including invasive fungal, parasitic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received LIFMIOR. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida*, *Pneumocystis, Aspergillus*, and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

#### Autoantibodies

Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheunatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with LIFMIOR (11%) than in Nacebotreated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with LIFMIOR compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of ratients treated with LIFMIOR compared to none of placebo-treated patients). The proportion of patients treated with LIFMIOR who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with LIFMIOR on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

#### Pancytopenia and aplastic anaemia

There have been postmarketing reports of pancy openia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

#### Interstitial lung disease

In controlled clinical trials of etaler ept cross all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled chinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and puln only fibrosis), some of which had fatal outcomes.

#### Concurrent treatment with anakinra

In studies when adult patients received concurrent treatment with LIFMIOR plus anakinra, a higher rate of set ous infections compared to LIFMIOR alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm<sup>3</sup>). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

#### Elerated liver enzymes

In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common).

#### Autoimmune hepatitis

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02%

(frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

#### Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediat is populations. Severe adverse events reported included varicella with signs and symptoms of ascetic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroene rith depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptor cell septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving LIFMIOR during 3 months of the dudy (part 1, open-label), and the frequency and severity of infections was similar in 58 patients of olding 12 months of open-label extension therapy. The types and proportion of adverse eye uvenile idiopathic arthritis patients were similar to those seen in trials of LIFMIOR in adul patients with rheumatoid arthritis, and the majority were mild. Several adverse events w more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of AIOR compared to the 349 adult rheumatoid arthritis patients. These included headache atients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (1%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation and ome in juvenile idiopathic arthritis clinical trials.

There have been reports of inflammatory bow disease and uveitis in JIA patients being treated with LIFMIOR from post-marketing sources, including a very small number of cases indicating a positive rechallenge (see section 4.4).

*Undesirable effects in paedical chiefients with plaque psoriasis* 

In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

#### Reporting of sus, ected a verse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued pronitoring 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.

#### **Overdose**

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m<sup>2</sup> followed by subcutaneous doses of 16 mg/m<sup>2</sup> administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg LIFMIOR subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to LIFMIOR.

#### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF- $\alpha$ ) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). By in TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulars TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etapercept, possess a higher affinity for TNF than monomeric receptors and are considerably more possess to competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglob can Fc region as a fusion element in the construction of a dimeric receptor imparts a longer sorum half-life.

#### Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ank tooing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecule, that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-modited cellular responses by rendering TNF biologically inactive. Etanercept may also mode ate ciologic responses controlled by additional downstream molecules (e.g., cytokines, adjustion molecules, or proteinases) that are induced or regulated by TNF.

#### Clinical efficacy and safety

This section presents data from four andomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankylosing spondylitis, one study in adults with non-radiographic axial spondyloarthritis, four studies in adults with plaque psoriasis, three studies in juvenile ideapathic arthritis and one study in paediatric patients with plaque psoriasis.

#### Adult patients with rheus atoid arthritis

The efficacy of NFMIOR was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 23# adult patients with active rheumatoid arthritis who had failed therapy with at least one but ne more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg LXIMIOR or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid athritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with LIFMIOR at 3 and 6 months than in patients treated with placebo (ACR 20: LIFMIOR 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: LIFMIOR 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; p<0.01 LIFMIOR vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

Approximately 15% of subjects who received LIFMIOR achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving LIFMIOR, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. LIFMIOR was significantly better than placebo in all components of the

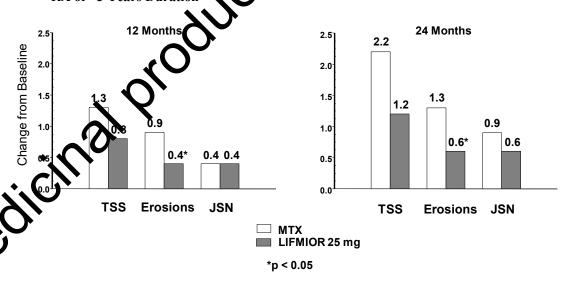
ACR criteria, as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with LIFMIOR compared to controls at 3 and 6 months.

After discontinuation of LIFMIOR, symptoms of arthritis generally returned within a month. Re-introduction of treatment with LIFMIOR after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received LIFMIOR without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received LIFMIOR without interruption.

The efficacy of LIFMIOR was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Poses of 10 mg or 25 mg LIFMIOR were administered subcutaneously (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, included conset of action within 2 weeks with LIFMIOR 25 mg, was similar to that seen in the previous trials and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with LIFMIOR 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (1 ss) han 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 1, 12, and 24 months. The 10 mg LIFMIOR dose had consistently less effect on structural damage than the 25 mg dose. LIFMIOR 25 mg was significantly superior to methotrexate forch sion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and LIFMIOR 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of LIFMIOR vs. Methotrexate in Patients with RA of <3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with LIFMIOR alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and the combination of LIFMIOR and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the LIFMIOR in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for LIFMIOR in combination with methotrexate compared with LIFMIOR monotherapy and methotrexate monotherapy were also observed after 24 months.

Clinical Efficacy Results at 12 Months: Comparison of LIFMIOR vs. Methotrexate vs. LIFMIOR in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years

|                             |              | Duration  |  |
|-----------------------------|--------------|-----------|--|
| Endpoint                    | Methotrexate | LIFMIOR   | LIFMIOR + • Methotrexate                       |
|                             | (n = 228)    | (n = 223) | (n = 231)                                      |
| ACR Responses <sup>a</sup>  |              |           | .,,0   |
| ACR 20                      | 58.8%        | 65.5%     | 74.5% <sup>†</sup> *                           |
| ACR 50                      | 36.4%        | 43.0%     | 63.2%  |
| ACR 70                      | 16.7%        | 22.0%     | 36.300   |
| DAS                         |              |           | •  |
| Baseline score <sup>b</sup> | 5.5          | 5.7       | 5.5  |
| Week 52 score <sup>b</sup>  | 3.0          | 3.0       | 2.3 <sup>†, φ</sup>                            |
| Remission <sup>c</sup>      | 14%          | 18%       | 2.3 <sup>†,\phi</sup><br>37% <sup>†,\phi</sup> |
| HAQ                         |              |           |  |
| Baseline                    | 1.7          | 1.7       | 1.8  |
| Week 52                     | 1.1          | 1.0       | $0.8^{\dagger,\phi}$                           |

a: Patients who did not complete 12 months in the study were considered to be non-responders.

Medicinal

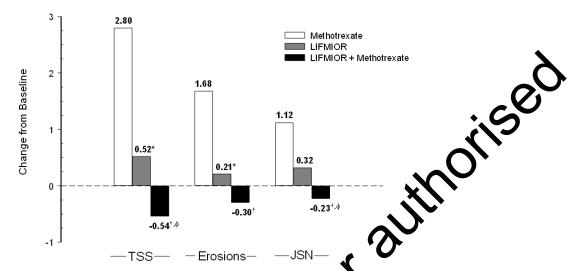
Radiographic progression at 12 members was significantly less in the LIFMIOR group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

b: Values for Disease Activity Score (DAS) are Leans.

c: Remission is defined as DAS < 1.6.

Pairwise comparison p-values:  $\dagger = p < 0.05$  for comparisons of LIFMIOR + methotrexate vs. methotrexate and  $\phi = p < 0.05$  for comparisons of LIFMIOR + methotrexate vs. LIFMIOR.

# Radiographic Progression: Comparison of LIFMIOR vs. Methotrexate vs. LIFMIOR in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: \* = p < 0.05 for comparisons of LIFMIOR vs. methotrexate, † = p < 0.05 for comparisons of LIFMIOR + methotrexate vs. methotrexate and  $\phi$  = p < 0.05 for comparisons of LIFMIOR + methotrexate vs. LIFMIOR.

Significant advantages for LIFMIOR in combination with neth trexate compared with LIFMIOR monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for LIFMIOR monotherapy dompared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change  $\leq 0.5$ ) at 24 months was higher in the LIFMIOR in combination with methotrexate group compared with the LIFMIOR alone and methotrexate alone groups (6.%, 50%, and 36%, respectively; p<0.05). The difference between LIFMIOR alone and methotrexate alone was also significant (p<0.05). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg LIFMIOR (two 25 mg SC injections) administered once weekly were evaluated into double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg LIFMIOR once weekly and 153 patients received 25 mg LIFMIOR twice weekly. The safety and efficacy profiles of the two LIFMIOR treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; that at week 16 did not show comparability (non-inferiority) between the two regimens. A single 50 mg/ml injection of LIFMIOR was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

Adult patients with psoriatic arthritis

The efficacy of LIFMIOR was assessed in a randomised, double-blind, placebo-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 70 years of age and had active psoriatic arthritis ( $\geq 3$  swollen joints and  $\geq 3$  tender joints) in at least one of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asymmetric psoriatic arthritis; or (5) spondylitis-like ankylosis. Patients also had plaque psoriasis with a qualifying target lesion  $\geq 2$  cm in diameter. Patients had previously been treated with NSAIDs (86%), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therapy (stable for  $\geq 2$  months) could

continue at a stable dose of ≤ 25 mg/week methotrexate. Doses of 25 mg of LIFMIOR (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered SC twice a week for 6 months. At the end of the double-blind study, patients could enter a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 Jithorised response and percentages with improvement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table below.

| Responses | of Patients with | Psoriatic Arthritis in a |
|-----------|------------------|--------------------------|
|           | Placeho-Contr    | olled Trial              |

| ntrolled Trial |                                       |
|----------------|---------------------------------------|
| Percent        | of Patients                           |
| Placebo        | LIFMIOR <sup>a</sup>                  |
| n = 104        | n = 101                               |
|                |                                       |
| 15             | 59 <sup>b</sup><br>50 <sup>b</sup>    |
| 13             | 50 <sup>b</sup>                       |
|                | 4                                     |
| 4              |                                       |
| 4              | <b>√</b> 3 <sup>6</sup>               |
| •              |                                       |
| 0              | 11 <sup>b</sup>                       |
| 10.            | 9°                                    |
| <b>^</b>       |                                       |
| 31             | 72 <sup>b</sup>                       |
| 23             | 70 <sup>b</sup>                       |
|                | Percent Placebo n = 104  15 13  4 4 3 |

a: 25 mg LIFMIOR SC wice weekly b: p < 0.001, LIFMI •lacebo

c: p < 0.01, LIFMIN

Among patients with psoriatic a three who received LIFMIOR, the clinical responses were apparent and were maintained through 6 months of therapy. LIFMIOR at the time of the first visit ( was significantly better than bbo in all measures of disease activity (p < 0.001), and responses were similar with and ut concomitant methotrexate therapy. Quality of life in psoriatic arthritis ery timepoint using the disability index of the HAQ. The disability index proved at all timepoints in psoriatic arthritis patients treated with LIFMIOR, antly i

hanges were assessed in the psoriatic arthritis study. Radiographs of hands and wrists at baseline and months 6, 12, and 24. The modified TSS at 12 months is presented in ble below. In an analysis in which all patients who dropped out of the study for any reason were ered to have progressed, the percentage of patients without progression (TSS change  $\leq 0.5$ ) at nonths was higher in the LIFMIOR group compared with the placebo group (73% vs. 47%, respectively,  $p \le 0.001$ ). The effect of LIFMIOR on radiographic progression was maintained in patients who continued on treatment during the second year. The slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

|          | Placebo     | Etanercept                |
|----------|-------------|---------------------------|
| Time     | (n = 104)   | (n = 101)                 |
| Month 12 | 1.00 (0.29) | -0.03 (0.09) <sup>a</sup> |

SE = standard error.

LIFMIOR treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of LIFMIOR in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.

No study has been performed in patients with psoriatic arthritis using the 50 mg once-weekly dosing regimen. Evidence of efficacy for the once-weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

#### Adult patients with ankylosing spondylitis

The efficacy of LIFMIOR in ankylosing spondylitis was assessed in 3 r ed, double-blind studies comparing twice-weekly administration of 25 mg LIFMIOR w cebo. A total of 401 patients were enrolled, from which 203 were treated with LIFMIOR Targest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age lctive ankylosing spondylitis defined as visual analog scale (VAS) scores of  $\geq 30$  for average duration and intensity of morning stiffness plus VAS scores of  $\geq 30$  for at least 2 of the following parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Function Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continu lem on stable doses. Patients with complete ankylosis of the spine were not included in the ady. Doses of 25 mg of LIFMIOR (based on dose-finding studies in patients with rheum toid arthritis) or placebo were administered subcutaneously twice a week for 6 mont 38 patients.

The primary measure of efficacy (ASAS 20) was a ≥20% improvement in at least 3 of the 4 Assessment in Ankylosing Spor dyntis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and the same of deterioration in the remaining domain. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% improvement, respectively.

Compared to placebootrea ment with LIFMIOR resulted in significant improvements in the ASAS 20, ASAS 50 and ASAS 70 is early as 2 weeks after the initiation of therapy.

a. p = 0.0001.

|                        | controlled Trial Percent of Patients |                 |  |  |
|------------------------|--------------------------------------|-----------------|--|--|
| Ankylosing Spondylitis | Placebo                              | LIFMIOR         |  |  |
| Response               | N = 139                              | N = 138         |  |  |
| ASAS 20                |                                      |                 |  |  |
| 2 weeks                | 22                                   | 46 <sup>a</sup> |  |  |
| 3 months               | 27                                   | 60 <sup>a</sup> |  |  |
| 6 months               | 23                                   | 58ª             |  |  |
| ASAS 50                |                                      |                 |  |  |
| 2 weeks                | 7                                    | 24ª             |  |  |
| 3 months               | 13                                   | 45ª             |  |  |
| 6 months               | 10                                   | 42ª             |  |  |
| ASAS 70                |                                      |                 |  |  |
| 2 weeks                | 2                                    | 12 <sup>b</sup> |  |  |
| 3 months               | 7                                    | 29 <sup>b</sup> |  |  |
| 6 months               | 5                                    | 28 <sup>b</sup> |  |  |

Among patients with ankylosing spondylitis who received LIFMIOL the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not received, concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spendylitis trials.

In a fourth study, the safety and efficacy of 50 mg 1 LMIOR (two 25 mg SC injections) administered once weekly vs. 25 mg LIFMIOR administered tyice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients was active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once-weekly and 25 mg twice-weekly regimens were similar.

Adult patients with non-radiographic ax al spondyloarthritis

The efficacy of LIFMIOR in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified at ant-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients useting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received LIFMIOR 50 mg, weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) was a 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. The double-blind period was followed by an open-label period during which all patients receive LIFMIOR 50 mg weekly for up to an additional 92 weeks. MRIs of the sacroiliac joint and spine were obtained to assess inflammation at baseline and at weeks 12 and 104.

Compared to placebo, treatment with LIFMIOR resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

## Efficacy Response in Placebo-Controlled nr-AxSpa Study: Percent of Patients Achieving Endpoints

| Double-Blind Clinical  | Placebo       | LIFMIOR           |
|------------------------|---------------|-------------------|
| Responses at Week 12   | N=106 to 109* | N=103 to 105*     |
| ASAS** 40              | 15.7          | 32.4 <sup>b</sup> |
| ASAS 20                | 36.1          | 52.4°             |
| ASAS 5/6               | 10.4          | 33.0ª             |
| ASAS partial remission | 11.9          | 24.8°             |
| BASDAI***50            | 23.9          | 43.8 <sup>b</sup> |

- \*Some patients did not provide complete data for each endpoint
- \*\*ASAS=Assessments in Spondyloarthritis International Society
- \*\*\*Bath Ankylosing Spondylitis Disease Activity Index
- a: p <0.001, b:<0.01 and c:<0.05, respectively between LIFMIOR and placebo

At week 12, there was a statistically significant improvement in the SPARCC (Spondyloa hrits Research Consortium of Canada) score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving LIFMIOR. Adjusted mean change from baseline was 3.8 for LIFMIOR treated (n=95) versus 0.8 for placebo treated (n=105) patients (p<0.001). At week 104, the mean Change from baseline in the SPARCC score measured on MRI for all LIFMIOR-treated subjects was 4.64 for the SIJ (n=153) and 1.40 the spine (n=154).

LIFMIOR showed statistically significantly greater improvement from besolve to week 12 compared to placebo in most health-related quality of life and physical function as assessments, including BASFI (Bath Ankylosing Spondylitis Functional Index), EuroQol 5D Gven II Health State Score and SF-36 Physical Component Score.

Clinical responses among nr-AxSpa patients who received NFMIOR were apparent at the time of the first visit (2 weeks) and were maintained through 2 can of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the midified New York Radiological Grade, indicative of axial spondyloarthropathy.

Adult patients with plaque psoria is

LIFMIOR is recommended for use a patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the three major systemic therapies as available.

The efficacy of NFMIOR versus other systemic therapies in patients with moderate to severe psoriasis (responsive to the responsive terms of the respon

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis involving  $\geq 10\%$  of the body surface area who were  $\geq 18$  years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of LIFMIOR (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. LIFMIOR was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three LIFMIOR doses. After 12 weeks of treatment,

patients in the placebo group began treatment with blinded LIFMIOR (25 mg twice a week); patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg LIFMIOR, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg LIFMIOR twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg LIFMIOR or placebo once weekly for 12 weeks and then all patients received open-label 50 mg LIFMIOR once weekly for an additional 12 weeks.

In study 1, the LIFMIOR-treated group had a significantly higher proportion of patients with a PAS 75 response at week 12 (30%) compared to the placebo-treated group (2%) (p<0.0001). At 24 vee's 56% of patients in the LIFMIOR-treated group had achieved the PASI 75 compared to 50 of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 and

|                     |         | Study 2 |                 |       |                 |         | Study 3 |          | . 0     | Study 4 |                    |
|---------------------|---------|---------|-----------------|-------|-----------------|---------|---------|----------|---------|---------|--------------------|
|                     |         |         | LIFN            | MIOR- |                 |         | LIFMIOR |          |         | LIFN    | MIOR               |
|                     |         | 25      | mg              | 50    | mg              |         | 25 mg   | 50 mg    |         | 50 mg   | 50 mg              |
|                     | Placebo | BI      | W               | BI    | W               | Placebo | BIW     | PW       | Placebo | QW      | QW                 |
|                     | n = 166 | n=      | n =             | n =   | n =             | n = 193 | n=196   | 1 = 16   | n = 46  | n = 96  | n = 90             |
|                     | wk 12   | 162     | 162             | 164   | 164             | wk 12   | wk 12.  | wk 19    | wk 12   | wk 12   | wk 24 <sup>a</sup> |
| Respons             |         | wk      | wk              | wk    | wk              |         |         | <b>\</b> |         |         |                    |
| e (%)               |         | 12      | 24 <sup>a</sup> | 12    | 24 <sup>a</sup> |         | V       |          |         |         |                    |
| PASI 50             | 14      | 58*     | 70              | 74*   | 77              | 9       | 64*     | 77*      | 9       | 69*     | 83                 |
| PASI 75             | 4       | 34*     | 44              | 49*   | 59              | 3       | 34*     | 49*      | 2       | 38*     | 71                 |
| DSGA <sup>b</sup> , |         |         |                 |       |                 | 1       |         |          |         |         |                    |
| clear or            |         |         |                 |       | •               | \'      |         |          |         |         |                    |
| almost              |         |         |                 |       | ~               |         |         |          |         |         |                    |
| clear               | 5       | 34*     | 39              | 49*   | 55              | 4       | 39*     | 57*      | 4       | 39*     | 64                 |

<sup>\*</sup> $p \le 0.0001$  compared with placebo

a. No statistical comparisons to place were made at week 24 in studies 2 and 4 because the original placebo group began receiving LFM IOR 25 mg BIW or 50 mg once weekly from week 13 to week 24. b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with laque psoriasis who received LIFMIOR, significant responses relative to placebo were apparent to the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 al o had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at has hair of the improvement achieved between baseline and week 24). During the withdrawal period, syn otoms of psoriasis gradually returned, with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with LIFMIOR in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their LIFMIOR dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the LIFMIOR-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) (p<0.0001). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where LIFMIOR was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

#### Antibodies to LIFMIOR

Antibodies to etanercept have been detected in the sera of some subjects treated with etan cept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with deumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spond, but, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanorce, t in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients ecceived 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each as essment point was up to approximately 9%.

#### Paediatric population

Paediatric patients with juvenile tampathic arthritis

The safety and efficacy of I were assessed in a two-part study in 69 children with pathic arthritis who had a variety of juvenile idiopathic arthritis onset polyarticular-course juvenile thritis, systemic onset). Patients aged 4 to 17 years with moderately to types (polyarthritis, paucia severely active polyaticul pr-course juvenile idiopathic arthritis refractory to, or intolerant of, ed; patients remained on a stable dose of a single nonsteroidal drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients g kg (maximum 25 mg per dose) LIFMIOR subcutaneously twice weekly. In part 2, with a clinical response at day 90 were randomised to remain on LIFMIOR or receive placebo ths and assessed for disease flare. Responses were measured using the ACR Pedi 30,  $\ge 30\%$  improvement in at least three of six and  $\ge 30\%$  worsening in no more than one of six ore set criteria, including active joint count, limitation of motion, physician and patient/parent al assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare vas defined as a  $\geq 30\%$  worsening in three of six JRA core set criteria and  $\geq 30\%$  improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on LIFMIOR experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was  $\geq$  116 days for patients who received LIFMIOR and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on LIFMIOR continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive LIFMIOR for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of LIFMIOR monotherapy (n=103), LIFMIOR plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study, 60 patients with extended oligoarthritis (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were theated with LIFMIOR at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued LIFMIOR therapy in patients who do not respond within 3 means of initiating LIFMIOR therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of LIFMIOR following its long-term use in patients with JIA.

#### Paediatric patients with plaque psoriasis

The efficacy of LIFMIOR was assessed in a randomised, double blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to evere plaque psoriasis (as defined by an sPGA score  $\geq$  3, involving  $\geq$  10% of the BSA, and PAS  $\geq$  12). Eligible patients had a history of receiving phototherapy or systemic therapy, or wave padequately controlled on topical therapy.

Patients received LIFMIOR 0.8 mg/kg (up \$\frac{1}{2}\$ 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to LIFMIOR had positive efficacy responses (e.g., PASI 75) than those randomised to placebo.

#### Paediatrik Plaque Psoriasis Outcomes at 12 Weeks

| 16/0                            | LIFMIOR<br>0.8 mg/kg Once<br>Weekly<br>(N = 106) | Placebo<br>(N = 105) |
|---------------------------------|--|----------------------|
| PASI 75, n (%)                  | 60 (57%) <sup>a</sup>                            | 12 (11%)             |
| PASI 50, n (6)                  | 79 (75%) <sup>a</sup>                            | 24 (23%)             |
| sPGA "dear" or "minimal", n (%) | 56 (53%) <sup>a</sup>                            | 14 (13%)             |

Abbreviation: sPGA-static Physician Global Assessment

p < 0.0001 compared with placebo

After the 12-week double-blind treatment period, all patients received LIFMIOR 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to LIFMIOR. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of LIFMIOR 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to

2 years beyond the 48 week study discussed above. Long-term experience with LIFMIOR was generally comparable to the original 48-week study and did not reveal any new safety findings.

#### 5.2 Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products, as well as the parent compound.

#### Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice-weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg LIFMIOR, the are regarded maximum serum concentration observed in healthy volunteers was  $1.65 \pm 0.66 \,\mu\text{g/ml}$ , and the treat under the curve was  $235 \pm 96.6 \,\mu\text{g} \cdot \text{hr/ml}$ .

Mean serum concentration profiles at steady state in treated RA patients were  $C_{max}$  of 2. kmg/l vs. 2.6 mg/l,  $C_{min}$  of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mg/m to 20 mg LIFMIOR once weekly (n=21) vs. 25 mg LIFMIOR twice weekly (n=16), respect very. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simple nearest injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondy its panelts, the etanercept steady state AUCs were 466  $\mu$ g•hr/ml and 474  $\mu$ g•hr/ml for 50 mg LYMIOR once weekly (N = 154) and 25 mg twice weekly (N = 148), respectively.

#### Distribution

A biexponential curve is required to describe the corner ration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

#### Elimination

Etanercept is cleared slowly from the took. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with theumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of LIFMIOR in rheumatoid arthritis patients and blasing spondylitis and plaque psoriasis patients are similar.

There is no apparent phorn acokinetic difference between males and females.

#### Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

#### Special populations

#### enal impairment

Alt ough there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

#### Hepatic impairment

Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

#### Elderly

The impact of advanced age was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

#### Paediatric population

Paediatric patients with juvenile idiopathic arthritis

In a polyarticular-course juvenile idiopathic arthritis trial with LIFMIOR, 69 patients (aged 4 to 17 years) were administered 0.4 mg LIFMIOR/kg twice weekly for three months. Serum concentration, profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

#### Paediatric patients with plaque psoriasis

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered (2.0 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks (Die mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks (2, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to be concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg et un cept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

#### 5.3 Preclinical safety data

In the toxicological studies with LIFMIOR, no dose anxiting or target organ toxicity was evident. LIFMIOR was considered to be non-genotoxic from battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with LIFMIOR due to the development of neutralising antibodies in rodents.

LIFMIOR did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg of a single intravenous dose of 1000 mg/kg. LIFMIOR did not elicit dose-limiting or target organ tox city in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 corp. Cative weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

#### 6. PHARMACNUTIČAL PARTICULARS

#### 6.1 List of excipients

Adam chloride
L-Arginine hydrochloride
Sodium phosphate monobasic dihydrate
Sodium phosphate dibasic dihydrate
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

30 months.

#### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

LIFMIOR may be stored at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks of removal from refrigeration.

Keep the pre-filled syringes in the outer carton in order to protect from light.

#### 6.5 Nature and contents of container

#### 25 mg solution for injection in pre-filled syringe

Clear glass syringe (type I glass) with stainless steel needle, rubber needle cover and plastic plunger. Cartons contain 4, 8 or 24 pre-filled syringes of LIFMIOR and 4, 8 or 24 alcohol swabs. The needle cover contains dry natural rubber (latex) (see section 4.4). Not all pack sizes hay be marketed.

#### 50 mg solution for injection in pre-filled syringe

Clear glass syringe (type I glass) with stainless steel needle, rubber needle cover and plastic plunger. Cartons contain 2, 4 or 12 pre-filled syringes of LIFMIOR with 2, 4 or 12 alcohol swabs. The needle cover contains dry natural rubber (latex) (see section 4.4). Not all pack sizes may be marketed.

#### 6.6 Special precautions for disposal and other landling

Before injection, LIFMIOR single-use pre-filled syringe should be allowed to reach room temperature (approximately 15 to 30 minutes). The needed cover should not be removed while allowing the pre-filled syringe to reach room temperature. The clution should be clear to slightly opalescent, colourless to pale yellow or pale brown, and may contain small translucent or white particles of protein.

Comprehensive instructions for administration are given in the package leaflet, section 7, "Instructions for preparation and giving at injection of LIFMIOR."

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

#### 7. MARKETING AUTHORISATION HOLDER

Pfizer Fixope MA EEIG Boultvarl de la Plaine 17 256 Bruxelles Belleium

ANTHORISATION/RENEWAL OF THE AUTHORISATION OF THE AUTHORISATION OF THE AUTHORISATION OF THE CHARLES AND AUTHORISATION OF THE TEXT

Detailed information on this medicinal product is available on the week of the Europea-Agency http://www.cma.curops.cu.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

#### 1. NAME OF THE MEDICINAL PRODUCT

LIFMIOR 50 mg solution for injection in pre-filled pen.

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 50 mg of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by scots binant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human tgG1. This Fc component contains the hinge, CH<sub>2</sub> and CH<sub>3</sub> regions, but not the CH<sub>1</sub> region of IgG). Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is 1.7 x 10<sup>6</sup> units/mg.

For the full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear, and colourless to pale yellow of pale brown.

#### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

#### Rheumatoid arthritis

LIFMIOR in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless convaindicated), has been inadequate.

LIFMIOR can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

LIFMIOI is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in a un not previously treated with methotrexate.

LIFMIOR, alone or in combination with methotrexate, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

#### Juvenile idiopathic arthritis

Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.

Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

LIFMIOR has not been studied in children aged less than 2 years.

#### Psoriatic arthritis

Treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. LIFMIOR 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.

#### Axial spondyloarthritis

#### Ankylosing spondylitis (AS)

Treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

#### Non-radiographic axial spondyloarthritis

Treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or hagretic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal atti-inflammatory drugs (NSAIDs).

#### Plaque psoriasis

Treatment of adults with moderate to severe plaque psorias, who failed to respond to, or who have a contraindication to, or are intolerant to other systemic merapy including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (see section 5.1).

#### Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis archildren and adolescents from the age of 6 years who are inadequately controlled by, or are intelerant to, other systemic therapies or phototherapies.

## 4.2 Posology and method of administration

LIFMIOR treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of theumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitic non-radiographic axial spondyloarthritis, plaque psoriasis or paediatric plaque psoriasis. Patient treate with LIFMIOR should be given the Patient Alert Card.

The LIFMIOR are filled pen is available in a 50 mg strength. Other presentations of LIFMIOR are available in strengths of 10 mg, 25 mg and 50 mg.

#### Poso ogy

#### Rhaimatoid arthritis

25 mg LIFMIOR administered twice weekly is the recommended dose. Alternatively, 50 mg administered once weekly has been shown to be safe and effective (see section 5.1).

Psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis

The recommended dose is 25 mg LIFMIOR administered twice weekly, or 50 mg administered once weekly.

For all of the above indications, available data suggest that a clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

#### Plaque psoriasis

The recommended dose of LIFMIOR is 25 mg administered twice weekly or 50 mg administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. Treatment with LIFMIOR should continue until remission is achieved, for up to 24 weeks. Continuous therapy beyond 24 weeks may be appropriate for some adult patients (see section 5.1). Treatment should be discontinued in patients who show no response after 12 weeks. If re-treatment with LIFMIOR is indicated, the same guidance on treatment duration should be followed. The dose should be 25 mg twice weekly or 50 mg once weekly.

#### Special populations

Renal and hepatic impairment
No dose adjustment is required.

#### Elderly

No dose adjustment is required. Posology and administration are the same as for a vills 18-64 years of age.

#### Paediatric population

The dosage of LIFMIOR is based on body weight for paediatric patients Padients weighing less than 62.5 kg should be accurately dosed on a mg/kg basis using the powder and solvent for solution for injection presentations or the powder for solution for injection presentations (see below for dosing for specific indication). Patients weighing 62.5 kg or more, may be dosed using a fixed-dose pre-filled syringe or pre-filled pen.

#### Juvenile idiopathic arthritis

The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose), given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.8 mg/kg (up to a maximum of 50 mg per dose) given once weekly. Discordinuation of treatment should be considered in patients who show no response after 4 months.

The 10 mg vial strength may be too appropriate for administration to children with JIA below the weight of 25 kg.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and older, when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of LIFMIOR in children aged below 2 years in the indication juvenile it lopathic arthritis.

Paed atril plaque psoriasis (age 6 years and above)

the recommended dose is 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be discontinued in patients who show no response after 12 weeks.

If re-treatment with LIFMIOR is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is generally no applicable use of LIFMIOR in children aged below 6 years in the indication plaque psoriasis.

#### Method of administration

LIFMIOR is administered by subcutaneous injection (see section 6.6).

Comprehensive instructions for administration are given in the package leaflet, section 7, "Using the MYCLIC pre-filled pen to inject LIFMIOR."

#### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with LIFMIOR should not be initiated in patients with active infections including chronic or localised infections.

#### 4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trademark and the basch number of the administered product should be clearly recorded (or stated) in the patients le.

#### Infections

Patients should be evaluated for infections before, during, and after treatment with 1 FMIOR, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections (including invasive fungal infections, listeriosis and legionellosis, have been reported with ne use of LIFMIOR (see section 4.8). These infections were due to bacteria, mycobacteria, fungi, virus s and parasites (including protozoa). In some cases, particular fungal and other opportunistic lafettions have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with LIFMIOR should be monitored closely. Administration of LIFMIOR should be discontinued if a patient develops a serious infection. The safety and efficacy of LIFMIOR in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of LIFMIOR in patients with a history of recurring or chronic infections of with underlying conditions that may predispose patients to infections such as advanced or poorly court all diabetes.

#### **Tuberculosis**

Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported in patients treated with LIFMIOR.

Before starting (reliment with LIFMIOR, all patients must be evaluated for both active and inactive ('latent') (belowings). This evaluation should include a detailed medical history with personal history of tubero losis or possible previous contact with tuberculosis and previous and/or current imminosuppressive therapy. Appropriate screening tests, i.e., tuberculin skin test and chest X-ray, sould be performed in all patients (local recommendations may apply). It is recommended that the confluct of these tests should be recorded in the patient's alert 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, LIFMIOR therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of LIFMIOR, and in accordance with local recommendations. In this situation, the benefit/risk balance of LIFMIOR therapy should be very carefully considered.

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 LIFMIOR treatment.

#### Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including LIFMIOR, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with LIFMIOR. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering LIFMIOR in patients previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Ade that data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, LIFMAR should be stopped and effective anti-viral therapy with appropriate supportive treatment should be attituded.

#### Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving LIFMIOR LIFMIOR should be used with caution in patients with a history of hepatitis C.

#### Concurrent treatment with anakinra

Concurrent administration of LIFMIOR and anakinra has been associated with an increased risk of serious infections and neutropenia compared to LIFMIOR along. This combination has not demonstrated increased clinical benefit. Thus the combined per of LIFMIOR and anakinra is not recommended (see sections 4.5 and 4.8).

#### Concurrent treatment with abatacept

In clinical studies, concurrent administration of about sept and LIFMIOR resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see action 4.5).

#### Allergic reactions

Allergic reactions associated with LFM OR administration have been reported commonly. Allergic reactions have included angioed ma and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction coders, LIFMIOR therapy should be discontinued immediately and appropriate therapy initiated.

The needle cap of the pre-illed pen contains latex (dry natural rubber) that may cause hypersensitivity reactions when handled to or when LIFMIOR is administered to persons with known or possible latex sensitivity.

#### Immusos opression

The pers bury exists for TNF-antagonists, including LIFMIOR, to affect host defences against infection) and malignancies since TNF mediates inflammation and modulates cellular immune is peases. In a study of 49 adult patients with rheumatoid arthritis treated with LIFMIOR, there was no lyidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue LIFMIOR therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of LIFMIOR in patients with immunosuppression have not been evaluated.

#### Malignancies and lymphoproliferative disorders

*Solid and haematopoietic malignancies (excluding skin cancers)* 

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. 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.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemic of other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy  $\leq$  18 years of age), including LIFMIOR, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rice radignancies typically associated with immunosuppression. A risk for the development of marignancies in children and adolescents treated with TNF-antagonists cannot be excluded

#### Skin cancers

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including LIFMIOR. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with LIFMIOR. Periodic skin examination is recommended for all patients, particularly losse with risk factors for skin cancer.

Combining the results of controlled climal rials, more cases of NMSC were observed in patients receiving LIFMIOR compared with control patients, particularly in patients with psoriasis.

#### **Vaccinations**

Live vaccines should not be viven concurrently with LIFMIOR. No data are available on the secondary transmission of infection by live vaccines in patients receiving LIFMIOR. In a double blind, placebo controlled, ra domised clinical study in adult patients with psoriatic arthritis 184 patients also received a multivalent preumococcal polysaccharide vaccine at week 4. In this study most psoriatic arthritis patients, equiving LIFMIOR were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titres in aggregate were moderately lower and few patients had two-fild lives in titres compared to patients not receiving LIFMIOR. The clinical significance of this is unsnown.

#### utcantibody formation

Trestment with LIFMIOR may result in the formation of autoimmune antibodies (see section 4.8).

#### Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with LIFMIOR. Caution should be exercised in patients being treated with LIFMIOR who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent fever, sore throat, bruising, bleeding, paleness) whilst on LIFMIOR, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, LIFMIOR should be discontinued.

#### Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with LIFMIOR (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating LIFMIOR therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing LIFMIOR to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

#### Combination therapy

In a controlled clinical trial of two years duration in rheumatoid arthritis patients, the combination of LIFMIOR and methotrexate did not result in unexpected safety findings, and the safety profile of LIFMIOR when given in combination with methotrexate was similar to the profiles report did studies of LIFMIOR and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of LIFMIOR in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of LIFMIOR in combination with other systemic therapies or photomerapy for the treatment of psoriasis has not been studied.

#### Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjust next is n eded in patients with renal or hepatic impairment; clinical experience in such patients is limited.

#### Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using LIFMIOR in patients who have congestive heart failure (CHF). There have been postmarketing reports of worse ling of CHF, with and without identifiable precipitating factors, in patients taking LIFMIOR. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients with all known pre-existing cardiovascular disease. Some of these patients have been under 50 years (Tage Two large clinical trials evaluating the use of LIFMIOR in the treatment of CHF were prelinated early due to lack of efficacy. Although not conclusive, data from one of these thals suggest a possible tendency toward worsening CHF in those patients assigned to LIFMIOR treatment.

#### Alcoholic hepatitis

In a phase II randomised b acebo-controlled study of 48 hospitalised patients treated with LIFMIOR or placebo for moderate o severe alcoholic hepatitis, LIFMIOR was not efficacious, and the mortality rate in patients treated with LIFMIOR was significantly higher after 6 months. Consequently, LIFMIOR shows that be used in patients for the treatment of alcoholic hepatitis. Physicians should use caution when using LIFMIOR in patients who also have moderate to severe alcoholic hepatitis.

#### Wegener granulomatosis

A placeb)-controlled trial, in which 89 adult patients were treated with LIFMIOR in addition to under therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown LIFMIOR to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with LIFMIOR than in the control group. LIFMIOR is not recommended for the treatment of Wegener's granulomatosis.

#### Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of LIFMIOR in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients.

#### Special populations

#### Elderly

In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who received LIFMIOR were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

#### Paediatric population

#### Vaccinations

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating LIFMIOR therapy (see Vaccinations, above).

Inflammatory bowel disease (IBD) and uveitis in patients with juvenile idiopathic arthritis (JIA) There have been reports of IBD and uveitis in JIA patients being treated with LIE. ICP (see section 4.8).

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

#### Concurrent treatment with anakinra

Adult patients treated with LIFMIOR and anakinra were observed a have a higher rate of serious infection when compared with patients treated with either LIFMOR or anakinra alone (historical data).

In addition, in a double-blind placebo-controlled trial in adult patients receiving background methotrexate, patients treated with LIFMIOR and an kirra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with LIFMIOR (see sections 4.4 and 4.8). The combination LIFMIOR and analy ra has not demonstrated increased clinical benefit and is therefore not recommended.

#### Concurrent treatment with abatacep

In clinical studies, concurrent administration of abatacept and LIFMIOR resulted in increased incidences of serious adverse are to. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

#### Concurrent treatment with sulfasalazine

In a clinical study of addit patients who were receiving established doses of sulfasalazine, to which LIFMIOR was a deal, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with LIFMIOR or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

#### on interactions

In dinical trials, no interactions have been observed when LIFMIOR was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfarin.

#### 4.6 Fertility, pregnancy and lactation

#### Women of childbearing potential

Women of childbearing potential should consider the use of appropriate contraception to avoid becoming pregnant during LIFMIOR therapy and for three weeks after discontinuation of therapy.

#### Pregnancy

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was No change in the rate of spontaneous abortion, stillbirth, or minor malformations was objective. another observational multi-country registry study comparing the risk of adverse pregr in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those non-biologic drugs (n=3497), there was no observed increased risk of major birt (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after country, maternal disease, parity, maternal age and smoking in early pregna (cy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth fections in the first year of life for infants born to women exposed to etanercept during pregnance 1 FMIOR should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the section of infants born to female patients treated with LIFMIOR during pregnancy. The clinical in part of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of LIFMIOR is generally not recommended.

#### Breast-feeding

Etanercept has been reported to be excreted in human milk following subcutaneous administration. In lactating rats following subcutaneous administration, etanercept was excreted in the milk and detected in the serum of pups. Because immune grabulins, in common with many medicinal products, can be excreted in human milk, a decision bust be made whether to discontinue breast-feeding or to discontinue LIFMIOR therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the worrest.

#### Fertility

Preclinical data about peri and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available.

#### 4.7 Effects of ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

#### **Undesirable effects**

#### Summary of the safety profile

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections, bronchitis, bladder infections and skin infections), allergic reactions, development of autoantibodies, itching, and fever.

Serious adverse reactions have also been reported for LIFMIOR. TNF-antagonists, such as LIFMIOR, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with LIFMIOR. Reports have included

fatal and life-threatening infections and sepsis. Various malignancies have also been reported with use of LIFMIOR, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have also been reported. These include rare reports of pancytopenia and very rare reports of aplastic anaemia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with LIFMIOR use. There have been rare reports of lupus, lupus-related conditions, and vasculitis.

#### Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials in adults and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ( $\geq$  (10) common ( $\geq$ 1/100 to <1/10); uncommon ( $\geq$ 1/1,000 to <1/100); rare ( $\geq$ 1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10   | Common ≥ 1/100 to < 1/10  | Uncommon<br>≥ 1/1,000 to < 1/100  | Rare ≥ 1/10,000 to < 1/1,000  | 000                  | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|--|---|---|---|----------------------|--|
| Infections and infestations   | Infection (including upper respiratory tract infection, bronchitis, cystitis, skin infection)* |   | Serious infections<br>(including<br>pneumonia,<br>cellulitis, arthritis<br>bacterial, sepsis and<br>parasitic infection)* | Tuberculcus, opportrists infection (nuclearing invarive fungal, proto bal, bacterial, atypical mycobacterial, viral infections, and Legionella)*  |                      | Hepatitis B reactivation, listeria   |
| Neoplasms<br>benign,<br>malignant and<br>unspecified<br>(including cysts<br>and polyps) |  | X   | Nov melanoma skin<br>crezer* (see<br>ectio 4.4)   | Malignant melanoma<br>(see section 4.4),<br>lymphoma,<br>leukaemia  |                      | Merkel cell<br>carcinoma (see<br>section 4.4)                                |
| Blood and<br>lymphatic<br>system disorders  | •  | 100   | Thrombocytopenia,<br>anaemia,<br>leukopenia,<br>neutropenia   | Pancytopenia*   | Aplastic<br>anaemia* | Histiocytosis<br>haematophagic<br>(macrophage<br>activation<br>syndrome)*    |
| Immune system disorders   | 9  | Allergic<br>reactions (see<br>Skin and<br>subcutaneous<br>tissue<br>disorders),<br>autoantibody<br>formation* | Vasculitis<br>(including anti-<br>neutrophilic<br>cytoplasmic antibody<br>positive vasculitis)                            | Serious<br>allergic/anaphylactic<br>reactions (including<br>angioedema,<br>bronchospasm),<br>sarcoidosis  |                      | Worsening of<br>symptoms of<br>dermatomyositis                               |
| N (rvol v system  |  |   |   | CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory |                      |  |

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10  | Common ≥ 1/100 to < 1/10 | Uncommon<br>≥ 1/1,000 to < 1/100   | Rare<br>≥ 1/10,000 to<br>< 1/1,000   | Very Rare < 1/10,000             | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|---|--------------------------|--|--|----------------------------------|--|
|   |   |                          |  | demyelinating<br>polyneuropathy,<br>demyelinating<br>polyneuropathy, and<br>multifocal motor<br>neuropathy (see<br>section 4.4), seizure     |                                  |  |
| Eye disorders<br>Cardiac<br>disorders                         |   |                          | Uveitis, scleritis  Worsening of cardiac failure congestive (see section 4.4)  | New onset cardiac<br>failure congestive<br>(see section 4.4)   |                                  | Olis   |
| Respiratory,<br>thoracic, and<br>mediastinal<br>disorders     |   |                          | section 1.1)   | Interstitial lung<br>disease (including<br>pneumonitis and<br>pulmonary fibrosis)*   | J                                |  |
| Hepatobiliary disorders                                       |   |                          | Elevated liver enzymes*  | Autoimmune hepatitis*  | ,0,                              |  |
| Skin and<br>subcutaneous<br>tissue disorders                  |   | Pruritus, rash           | Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash | Stevens-Johnson<br>syndrome, cutate di<br>vasculitis (callio<br>hypersens tivit)<br>vasculitis, erythima<br>multiname, lichenoid<br>each ins | Toxic<br>epidermal<br>necrolysis |  |
| Musculoskeletal<br>and connective<br>tissue disorders         |   |                          | .,00   | erythematosus,<br>subacute cutaneous<br>lupus erythematosus,<br>lupus-like syndrome  |                                  |  |
| General<br>disorders and<br>administration<br>site conditions | Injection<br>site<br>reactions<br>(including<br>bleeding,<br>bruising,<br>erythema,<br>itching,<br>pain,<br>swelling) | Pyrexia                  |  |  |                                  |  |

<sup>\*</sup>see Description of selected ad the reactions, below.

#### Description of son sted adverse reactions

Malignaters and lymphoproliferative disorders

One functed and twenty-nine new malignancies of various types were observed in 4,114 rheumatoid with the patients treated in clinical trials with LIFMIOR for up to approximately 6 years, including 23 patients treated with LIFMIOR in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 LIFMIOR-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in LIFMIOR-treated patients. In a group of 2,711 plaque psoriasis patients treated with LIFMIOR in double-blind and open-label studies of up to 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with LIFMIOR in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

#### *Injection site reactions*

Compared to placebo, patients with rheumatic diseases treated with LIFMIOR had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the LIFMIOR treatment groups, and the majority of patients who were given treatment received topical preparations such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with LIFMIOR developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

#### Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serior nt ctions occurred in 6.3% s. These included abscess (at of rheumatoid arthritis patients treated with LIFMIOR for up to 48 man various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecysti arrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zost a, er, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis. septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and d infection. In the 2-year active-controlled study where patients were treated with either LIFMIOR alone, methotrexate alone or LIFMIOR in combination with methotrexate, the rat f serious infections were similar among the treatment groups. However, it cannot be excluded e combination of LIFMIOR with methotrexate could be associated with an increa e in the rate of infections.

There were no differences in rates of infection among patients treated with LIFMIOR and those treated with placebo for plaque psoriatis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by LYFM OR-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteoryelitis, gastritis, appendicitis, Streptococcal fasciitis, myositis, septic shock, diverticulitis and abscess to the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (anel monia).

Serious and fatal infections have been reported during use of LIFMIOR; reported pathogens include bacteria, mycobasteria (socluding tuberculosis), viruses and fungi. Some have occurred within a few weeks after injusting treatment with LIFMIOR in patients who have underlying conditions (e.g., diabetes, congenite heart failure, history of active or chronic infections) in addition to their rheumatoid arbiritis (see section 4.4). LIFMIOR treatment may increase mortality in patients with established appsis.

opertunistic infections have been reported in association with LIFMIOR, including invasive fungal, partistic (including protozoal), viral (including herpes zoster), bacterial (including *Listeria* and *Legionella*), and atypical mycobacterial infections. In a pooled data set of clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 subjects who received LIFMIOR. The exposure-adjusted rate was 0.06 events per 100 patient-years. In postmarketing experience, approximately half of all of the case reports of opportunistic infections worldwide were invasive fungal infections. The most commonly reported invasive fungal infections included *Candida*, *Pneumocystis, Aspergillus*, and *Histoplasma*. Invasive fungal infections accounted for more than half of the fatalities amongst patients who developed opportunistic infections. The majority of the reports with a fatal outcome were in patients with *Pneumocystis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.4).

#### Autoantibodies

Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) was higher in patients treated with LIFMIOR (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with LIFMIOR compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with LIFMIOR compared to none of placebo-treated patients). The proportion of patients treated with LIFMIOR who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with LIFMIOR on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and by one

#### Pancytopenia and aplastic anaemia

There have been postmarketing reports of pancytopenia and aplastic anaemia, som of hich had fatal outcomes (see section 4.4).

#### Interstitial lung disease

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without conformant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed conformant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been postmarketing separts of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had faral outcomes.

#### Concurrent treatment with anakinra

In studies when adult patients received concurred treatment with LIFMIOR plus anakinra, a higher rate of serious infections compared to LIFLYIOR afone was observed and 2% of patients (3/139) developed neutropenia (absolute neutropenia count < 1000/mm<sup>3</sup>). While neutropenic, one patient developed cellulitis that resolved after the pivalisation (see sections 4.4 and 4.5).

#### Elevated liver enzymes

In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concentrant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled lini al trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency accommon).

#### Autoimmuse hopatitis

In corpoled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autorum ne hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (a equency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).

#### Paediatric population

Undesirable effects in paediatric patients with juvenile idiopathic arthritis
In general, the adverse events in paediatric patients with juvenile idiopathic arthritis were similar in frequency and type to those seen in adult patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving LIFMIOR during 3 months of the study (part 1, open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of LIFMIOR in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 60 juvenile idiopathic arthritis patients receiving 3 months of LIFMIOR compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arranges clinical trials.

There have been reports of inflammatory bowel disease and uveitis in JLAs alients being treated with LIFMIOR from post-marketing sources, including a very small number access indicating a positive rechallenge (see section 4.4).

Undesirable effects in paediatric patients with plaque psoriasis. In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit isk 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 dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m² followed by subcutaneous doses of 16 mg/m² administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg LIFMIOR subcutaneously twice weekly for 3 weeks without experiencing unless table effects. There is no known antidote to LIFMIOR.

#### 5. Pharmacological properties

#### Pharmacodynamic properties

marmacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF- $\alpha$ ) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF-binding to its cell surface receptors and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55)

and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors such as etanercept possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

## Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by addational downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are independent regulated by TNF.

## Clinical efficacy and safety

This section presents data from four randomised controlled trials in adults with rheumatoid arthritis, one study in adults with psoriatic arthritis, one study in adults with ankyloring spondylitis, one study in adults with non-radiographic axial spondyloarthritis, four studies in a dit with plaque psoriasis, three studies in juvenile idiopathic arthritis and one study in paediat ic patients with plaque psoriasis.

## Adult patients with rheumatoid arthritis

The efficacy of LIFMIOR was assessed in a randomised, double blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid a thritis who had failed therapy with at least one but no more than four disease-modifying antirhedinatic drugs (DMARDs). Doses of 10 mg or 25 mg LIFMIOR or placebo were administered subc tareously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in oalents treated with LIFMIOR at 3 and 6 months than in patients treated with placebo (ACR 20: NFMIOR 62% and 59%, placebo 23% and 11% at 3 and 6 months respectively: ACR 50: LINVIOR 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; p<0.01 LIFMIOR 3. Placebo at all timepoints for both ACR 20 and ACR 50 responses).

Approximately 15% of subjects who received LIFMIOR achieved an ACR 70 response at month 3 and month 6 compared to lewer than 5% of subjects in the placebo arm. Among patients receiving LIFMIOR, the chiqical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always a suited by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. LIFMIOR was significantly better than placebo in all components of the ACR criteria as well as other measures of rheumatoid arthritis disease activity not included in the ACR response spiteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included lisability, vitality, mental health, general health status, and arthritis-associated health status abdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with LIFMIOR compared to controls at 3 and 6 months.

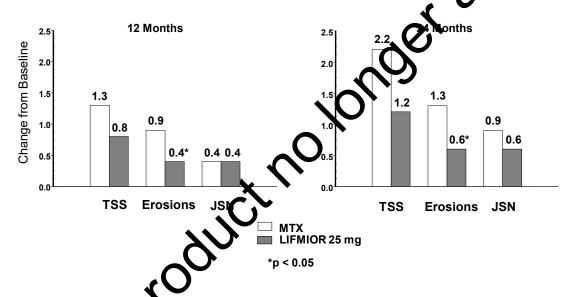
After discontinuation of LIFMIOR, symptoms of arthritis generally returned within a month. Re-introduction of treatment with LIFMIOR after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received LIFMIOR without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received LIFMIOR without interruption.

The efficacy of LIFMIOR was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of

10 mg or 25 mg LIFMIOR were administered SC twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with LIFMIOR 25 mg was similar to that seen in the previous trials, and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with LIFMIOR 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg LIFMIOR dose had consistently less effect on structural damage than the 25 mg dose. LIFMIOP 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and LYMX or 25 mg. The results are shown in the figure below.

Radiographic Progression: Comparison of LIFMIOR vs Methotrevate Patients with RA of <3 Years Duration



In another active-cont on a double-blind, randomised study, clinical efficacy, safety, and radiographic prepression in RA patients treated with LIFMIOR alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and of the combination of LIFMIOR and methotrexate distinct concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least a disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Take in the LIFMIOR in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 32 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for LIFMIOR in combination with methotrexate compared with LIFMIOR monotherapy and methotrexate monotherapy were also observed after 24 months.

## Clinical Efficacy Results at 12 Months: Comparison of LIFMIOR vs Methotrexate vs LIFMIOR in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration

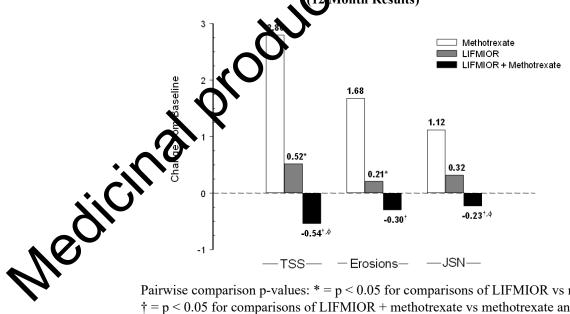
|                             |              |           | LIFMIOR +                            |
|-----------------------------|--------------|-----------|--------------------------------------|
| Endpoint                    | Methotrexate | LIFMIOR   | Methotrexate                         |
|                             | (n = 228)    | (n = 223) | (n = 231)                            |
| ACR Responses <sup>a</sup>  |              |           |                                      |
| ACR 20                      | 58.8%        | 65.5%     | 74.5% <sup>†, ф</sup>                |
| ACR 50                      | 36.4%        | 43.0%     | 63.2% <sup>†,ф</sup>                 |
| ACR 70                      | 16.7%        | 22.0%     | 39.8% <sup>†, ф</sup>                |
| DAS                         |              |           |                                      |
| Baseline score <sup>b</sup> | 5.5          | 5.7       | 5.5                                  |
| Week 52 score <sup>b</sup>  | 3.0          | 3.0       | 2.3 <sup>†, φ</sup>                  |
| Remission <sup>c</sup>      | 14%          | 18%       | 37% <sup>†,</sup>                    |
| HAQ                         |              |           |                                      |
| Baseline                    | 1.7          | 1.7       |                                      |
| Week 52                     | 1.1          | 1.0       | <b>6</b> .8 <sup>†, \( \phi \)</sup> |

a: Patients who did not complete 12 months in the study were considered to be on-responders.

Pairwise comparison p-values:  $\dagger = p < 0.05$  for comparisons of LII nethotrexate vs methotrexate and  $\phi = p < 0.05$  for comparisons of LIFMIOR + methotrexate

Radiographic progression at 12 months was significantly the LIFMIOR group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below)

## Radiographic Progression: Comparison of LIFMIOR vs Methotrexate vs LIFMIOR in Combination with Methotrexate in A tients with RA of 6 Months To 20 Years Duration onth Results)



Pairwise comparison p-values: \* = p < 0.05 for comparisons of LIFMIOR vs methotrexate,  $\dagger = p < 0.05$  for comparisons of LIFMIOR + methotrexate vs methotrexate and  $\phi =$ p < 0.05 for comparisons of LIFMIOR + methotrexate vs LIFMIOR

Significant advantages for LIFMIOR in combination with methotrexate compared with LIFMIOR monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the

b: Values for Disease Activity Score (DAS) are means.

c: Remission is defined as DAS < 1.6

significant advantages for LIFMIOR monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change  $\leq$  0.5) at 24 months was higher in the LIFMIOR in combination with methotrexate group compared with the LIFMIOR alone and methotrexate alone groups (62%, 50%, and 36%, respectively; p<0.05). The difference between LIFMIOR alone and methotrexate alone was also significant (p<0.05). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50 mg LIFMIOR (two 25 mg SC injections) administered once weekly, were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg LIFMIOR once weekly and 153 patients received 25 mg LIFMIOR twice weekly. The safety and efficacy profiles of the 160 LIFMIOR treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens. A single 50 mg/ml injection of LIFMIOR was found to be bioequivalent to two simultaneous hijections of 25 mg/ml.

## Adult patients with psoriatic arthritis

Medicinal

The efficacy of LIFMIOR was assessed in a randomised, double-bline o-controlled study in 205 patients with psoriatic arthritis. Patients were between 18 and 7 rs of age and had active psoriatic arthritis ( $\geq 3$  swollen joints and  $\geq 3$  tender joints) in at eas of the following forms: (1) distal interphalangeal (DIP) involvement; (2) polyarticula writis (absence of rheumatoid nodules and presence of psoriasis); (3) arthritis mutilans; (4) asylametric psoriatic arthritis; or (5) spondylitislike ankylosis. Patients also had plaque psoriasis with a qualitying target lesion  $\geq 2$  cm in diameter. Patients had previously been treated with NSAIDs (26%) ), DMARDs (80%), and corticosteroids (24%). Patients currently on methotrexate therap for  $\geq 2$  months) could continue at a stable dose of  $\leq 25$  mg/week methotrexate. Doses of 2 of LIFMIOR (based on dose-finding studies in patients with rheumatoid arthritis) or place were administered SC twice a week for 6 months. At the end of the double-blind study, patients Arer a long-term open-label extension study for a total duration of up to 2 years.

Clinical responses were expressed as percentages of patients achieving the ACR 20, 50, and 70 response and percentages with Exprovement in Psoriatic Arthritis Response Criteria (PsARC). Results are summarised in the table celov.

## Responses of Patients with Psoriatic Arthritis in a Placebo-Controlled Trial

| 1 lacebo-Col                 | iti oneu 111ai |                      |              |
|------------------------------|----------------|----------------------|--------------|
|                              | of Patients    |                      |              |
|                              | Placebo        | LIFMIOR <sup>a</sup> |              |
| Psoriatic Arthritis Response | n = 104        | n = 101              |              |
| ACR 20                       |                |                      |              |
| Month 3                      | 15             | 59 <sup>b</sup>      |              |
| Month 6                      | 13             | 50 <sup>b</sup>      |              |
| ACR 50                       |                |                      |              |
| Month 3                      | 4              | $38^{b}$             | 3/3          |
| Month 6                      | 4              | 37 <sup>b</sup>      | <b>%</b>     |
| ACR 70                       |                | ,                    |              |
| Month 3                      | 0              | 11 <sup>b</sup>      | <b>X</b> \ ' |
| Month 6                      | 1              | 9°                   |              |
| PsARC                        |                | <i>─</i>             |              |
| Month 3                      | 31             | <b>1</b> 0°          |              |
| Month 6                      | 23             |                      |              |
| a: 25 mg LIFMIOR SC twice w  | eekly          | V                    |              |

a: 25 mg LIFMIOR SC twice weekly b: p < 0.001, LIFMIOR vs. placebo

c: p < 0.01, LIFMIOR vs. placebo

Among patients with psoriatic arthritis who received LIFMLOR the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained brough 6 months of therapy. LIFMIOR was significantly better than placebo in all measures of lisease activity (p < 0.001), and responses were similar with and without concomitant methods, at therapy. Quality of life in psoriatic arthritis patients was assessed at every timepoint using the disability index of the HAQ. The disability index score was significantly improved at all time toints in psoriatic arthritis patients treated with LIFMIOR, relative to placebo (p < 0.001).

Radiographic changes were assessed in the psoriatic arthritis study. Radiographs of hands and wrists were obtained at baseline and months  $\mathfrak{b}$ , 12, and 24. The modified TSS at 12 months is presented in the Table below. In an analyzis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change  $\leq 0.5$ ) at 12 months was higher in the LIFMIOR group compared with the placebo group (73% vs. 47%, respectively,  $p \leq 0.00$  at 12. The effect of LIFMIOR on radiographic progression was maintained in patients who continued on treatment during the second year. The slowing of peripheral joint damage was observed in attents with polyarticular symmetrical joint involvement.

Mean (SE) Annualized Change from Baseline in Total Sharp Score

|          | Placebo     | Etanercept                |
|----------|-------------|---------------------------|
| Time     | (n = 104)   | (n = 101)                 |
| Month 12 | 1.00 (0.29) | -0.03 (0.09) <sup>a</sup> |

SE = standard error.

a. p = 0.0001.

LIFMIOR treatment resulted in improvement in physical function during the double-blind period, and this benefit was maintained during the longer-term exposure of up to 2 years.

There is insufficient evidence of the efficacy of LIFMIOR in patients with ankylosing spondylitis-like and arthritis mutilans psoriatic arthropathies due to the small number of patients studied.

No study has been performed in patients with psoriatic arthritis using the 50 mg once weekly dosing regimen. Evidence of efficacy for the once weekly dosing regimen in this patient population has been based on data from the study in patients with ankylosing spondylitis.

Adult patients with ankylosing spondylitis

The efficacy of LIFMIOR in ankylosing spondylitis was assessed in 3 randomised, double-blind studies comparing twice weekly administration of 25 mg LIFMIOR with placebo. A total of 401 patients were enrolled from which 203 were treated with LIFMIOR. The largest of these trials (n= 277) enrolled patients who were between 18 and 70 years of age and had active ankylosing spondylitis defined as visual analog scale (VAS) scores of ≥ 30 for average of duration and intensity of morning stiffness plus VAS scores of ≥ 30 for at least 2 of the following 3 parameters: patient global assessment; average of VAS values for nocturnal back pain and total back pain; average of 10 questions on the Bath Ankylosing Spondylitis Functional Index (BASFI). Patients receiving DMARDs, NSAIDS, or corticosteroids could continue them on stable doses. Patients with complete ankylosis of the spine were not included in the study. Doses of 25 mg of LIFMIOR (based on dose-finding studies in patients with rheumatoid arthritis) or placebo were administered subcutaneously twice a week for 6 months in 138 patients.

The primary measure of efficacy (ASAS 20) was a ≥20% improvement in at least 3 of the 4 Assessment in Ankylosing Spondylitis (ASAS) domains (patient global assessments, back pain, BASFI, and inflammation) and absence of deterioration in the remaining or main. ASAS 50 and 70 responses used the same criteria with a 50% improvement or a 70% is provement, respectively.

Compared to placebo, treatment with LIFMIOR resulted in significant provements in the ASAS 20, ASAS 50 and ASAS 70 as early as 2 weeks after the initiation of herapy.

| Responses of Patients with Ankylosing Spondylitis in a |                |                 |  |  |  |  |  |
|--|----------------|-----------------|--|--|--|--|--|
| Placebo-Con roned Trial Percent of Patients            |                |                 |  |  |  |  |  |
| 4  | <del>- 1</del> | +               |  |  |  |  |  |
|  | Placebo        | LIFMIOR         |  |  |  |  |  |
| Ankylosing Spondyliks                                  | $\sim$ N = 139 | N = 138         |  |  |  |  |  |
| Response   |                |                 |  |  |  |  |  |
| ASAS 20  |                |                 |  |  |  |  |  |
| 2 weeks  | 22             | 46 <sup>a</sup> |  |  |  |  |  |
| 3 months   | 27             | 60 <sup>a</sup> |  |  |  |  |  |
| 6 months   | 23             | 58ª             |  |  |  |  |  |
| ASAN 50  |                |                 |  |  |  |  |  |
| 2 veeks  | 7              | 24 <sup>a</sup> |  |  |  |  |  |
| 3 nonths   | 13             | 45 <sup>a</sup> |  |  |  |  |  |
| 6 months   | 10             | 42ª             |  |  |  |  |  |
| ASAS 70:   |                |                 |  |  |  |  |  |
| 2 weeks  | 2              | 12 <sup>b</sup> |  |  |  |  |  |
| 3 months   | 7              | 29 <sup>b</sup> |  |  |  |  |  |
| 6 months   | 5              | 28 <sup>b</sup> |  |  |  |  |  |
| a: p <0.001, LIFMIOR vs. Placebo                       |                |                 |  |  |  |  |  |
| b: p = 0.002, LIFMIOR vs. placebo                      |                |                 |  |  |  |  |  |

Among patients with ankylosing spondylitis who received LIFMIOR, the clinical responses were apparent at the time of the first visit (2 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant therapies at baseline.

Similar results were obtained in the 2 smaller ankylosing spondylitis trials.

In a fourth study, the safety and efficacy of 50 mg LIFMIOR (two 25 mg SC injections) administered once weekly vs 25 mg LIFMIOR administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The safety and efficacy profiles of the 50 mg once weekly and 25 mg twice weekly regimens were similar.

Adult patients with non-radiographic axial spondyloarthritis

The efficacy of LIFMIOR in patients with non-radiographic axial spondyloarthritis (nr-AxSpa) was assessed in a randomised, 12-week double-blind, placebo-controlled study. The study evaluated 215 adult patients (modified intent-to-treat population) with active nr-AxSpa (18 to 49 years of age), defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS. Patients were also required to have an inadequate response or intolerance to two or more NSAIDs. In the double-blind period, patients received LIFMIOR 50 mg weekly or placebo for 12 weeks. The primary measure of efficacy (ASAS 40) and 40% improvement in at least three of the four ASAS domains and absence of deterioration in the remaining domain. The double-blind period was followed by an open-label period during thic, all patients receive LIFMIOR 50 mg weekly for up to an additional 92 weeks. MRIs of the steroiliac joint and spine were obtained to assess inflammation at baseline and at weeks 12 and 104

Compared to placebo, treatment with LIFMIOR resulted in statistically significant improvement in the ASAS 40, ASAS 20 and ASAS 5/6. Significant improvement was also observed for the ASAS partial remission and BASDAI 50. Week 12 results are shown in the table below.

Efficacy Response in Placebo-Controlled nr-AxSpa Study: Lero et of Patients Achieving

|                        | Enupoints     |                   |
|------------------------|---------------|-------------------|
| Double-Blind Clinical  | Placeo        | LIFMIOR           |
| Responses at Week 12   | N=126 to 109* | N=103 to 105*     |
| ASAS** 40              | 13.7          | 32.4 <sup>b</sup> |
| ASAS 20                | 36.1          | 52.4°             |
| ASAS 5/6               | 10.4          | 33.0°             |
| ASAS partial remission | 11.9          | 24.8°             |
| BASDAI***50            | 23.9          | 43.8 <sup>b</sup> |

<sup>\*</sup>Some patients did not provide complete data for each endpoint

At week 12, there was a satistically significant improvement in the SPARCC (Spondyloarthritis Research Consortium of Canada) score for the sacroiliac joint (SIJ) as measured by MRI for patients receiving LIFMIOR. A linested mean change from baseline was 3.8 for LIFMIOR treated (n=95) versus 0.8 for place by treated (n=105) patients (p<0.001). At week 104, the mean change from baseline in the STARCC score measured on MRI for all LIFMIOR-treated subjects was 4.64 for the SIJ (n=153) and 3.40 the spine (n=154).

LIFN 10R showed statistically significantly greater improvement from baseline to week 12 compared to Nativo in most health-related quality of life and physical function assessments, including BASFI (Byth Ankylosing Spondylitis Functional Index), EuroQol 5D Overall Health State Score and SF-36 (Bysical Component Score.

Clinical responses among nr-AxSpa patients who received LIFMIOR were apparent at the time of the first visit (2 weeks) and were maintained through 2 years of therapy. Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy. The 2 year data did not reveal any new safety findings. At week 104, 8 subjects had progressed to a score of bilateral Grade 2 on spinal X-ray according to the modified New York Radiological Grade, indicative of axial spondyloarthropathy.

<sup>\*\*</sup>ASAS=Assessments in Spond Joarthritis International Society

<sup>\*\*\*</sup>Bath Ankylosing Spon All Disease Activity Index

a: p<0.001, b:<0.01 and c<0.05, respectively between LIFMIOR and placebo

Adult patients with plaque psoriasis

LIFMIOR is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the three major systemic therapies as available.

The efficacy of LIFMIOR versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing LIFMIOR with other systemic therapies. Instead, the safety and efficacy of LIFMIOR were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks

Study 1 was a Phase 2 study in patients with active but clinically stable plaque psoriasis it (olving  $\ge$  10% of the body surface area that were  $\ge$  18 years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of LIFMIOR (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PAST) 10 at screening. LIFMIOR was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double clind treatment period, patients received placebo or one of the above three LIFMIOR dose. After 12 weeks of treatment, patients in the placebo group began treatment with blinded LIFMOR (25 mg twice a week); patients in the active treatment groups continued to week 24 on the cose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients in this study received a dose of 25 mg or 50 mg LIFMIOR, & placebo twice a week for 12 weeks and then all patients received open-label 25 mg LIFMIOR twice weekly for an additional 24 weeks.

Study 4 evaluated 142 patients and had smiller inclusion criteria to studies 2 and 3. Patients in this study received a dose of 50 mg KFNIO cor placebo once weekly for 12 weeks and then all patients received open-label 50 mg LIFNIO conce weekly for an additional 12 weeks.

In study 1, the LIFMIOR-treated group had a significantly higher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) (p<0.0001). At 24 weeks, 56% of patients in the LIFMIOR-treated group had achieved the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2, 3 and 4 are shown below.

## Responses of Patients with Psoriasis in Studies 2, 3 And 4

|                     |         | Study 2 |                 |       |                 |         | Study 3 |         |         | Study 4      |                    |
|---------------------|---------|---------|-----------------|-------|-----------------|---------|---------|---------|---------|--------------|--------------------|
|                     |         |         | LIFN            | MIOR- |                 |         | LIFN    | MIOR    |         | LIFN         | MIOR               |
|                     |         | 25      | mg              | 50    | mg              |         | 25 mg   | 50 mg   |         | 50 mg        | 50 mg              |
|                     | Placebo | BI      | W               | BI    | W               | Placebo | BIW     | BIW     | Placebo | QW           | QW                 |
|                     | n = 166 | n=      | n =             | n =   | n =             | n = 193 | n = 196 | n = 196 | n = 46  | n = 96       | n = 90             |
|                     | wk 12   | 162     | 162             | 164   | 164             | wk 12        | wk 24 <sup>a</sup> |
| Respons             |         | wk      | wk              | wk    | wk              |         |         |         |         |              |                    |
| e (%)               |         | 12      | 24 <sup>a</sup> | 12    | 24 <sup>a</sup> |         |         |         |         |              |                    |
| PASI 50             | 14      | 58*     | 70              | 74*   | 77              | 9       | 64*     | 77*     | 9       | 69*          | 83                 |
| PASI 75             | 4       | 34*     | 44              | 49*   | 59              | 3       | 34*     | 49*     | 2       | 38*          | 71                 |
| DSGA <sup>b</sup> , |         |         |                 |       |                 |         |         |         |         |              | 11                 |
| clear or            |         |         |                 |       |                 |         |         |         |         | (            | 7,                 |
| almost              |         |         |                 |       |                 |         |         |         |         |              |                    |
| clear               | 5       | 34*     | 39              | 49*   | 55              | 4       | 39*     | 57*     | 4       | <b>X</b> 33* | 64                 |

<sup>\*</sup> $p \le 0.0001$  compared with placebo

Among patients with plaque psoriasis who received LIFMIOR, sign fit at responses relative to placebo were apparent at the time of the first visit (2 weeks) and are the intended through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis placed serious adverse events were observed. There was some evidence to support a benefit of re-trealment with LIFMIOR in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their LIFMIOR dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the LIFMIOR-freated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) (p<0.0001). For patients who received 50 mg once weekly throughout the study, the efficacy responses continued to improve with 71% achieving PASI 75 at week 14.

In long term (up to 34 months) open-label studies where LIFMIOR was given without interruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or continuous). Consequently, the choice of intermittent or continuous therapy should be based upon physician judgment and individual patient needs.

## Antibodies to LIFMIOR

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving LIFMIOR 25 mg BIW or 50 mg once weekly from Week 13 to week 24.

b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 10 a 0 to 5 scale.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with paediatric psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

## Paediatric population

Paediatric patients with juvenile idiopathic arthritis

The safety and efficacy of LIFMIOR were assessed in a two-part study in 69 children polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types (polyarthritis, pauciarthritis, systemic onset). Patients aged 4 to 17 with moderately to to, or intolerant of, severely active polyarticular-course juvenile idiopathic arthritis refrag methotrexate were enrolled; patients remained on a stable dose of a sing nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 limum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) LIFMIOR s neously twice weekly. In part 2, patients with a clinical response at day 90 were randomixed o remain on LIFMIOR or receive placebo for four months and assessed for disease flare. Responses were measured using the ACR Pedi 30, defined as  $\ge 30\%$  improvement in at least three of six and  $\ge 30\%$  worsening in no more than one of six JRA core set criteria, including active joint count ion of motion, physician and patient/parent global assessments, functional assessment, and with ocyte sedimentation rate (ESR). Disease flare was defined as a  $\geq 30\%$  worsening in three of six JRA core set criteria and  $\geq 30\%$  improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (7%), patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on LIFMIOR experienced a disease flare compared to 20 of 26 (77%) patients receiving that E = (p=0.007). From the start of part 2, the median time to flare was  $\geq$  116 days for patients who received LIFMIOR and 28 days for patients who received placebo. Of patients who demonstrated clinical response at 90 days and entered part 2 of the study, some of the patients remaining on LIFMIOR continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-labe Cafety extension study, 58 paediatric patients from the above study (from the age of 4 years at three of enrolment) continued to receive LIFMIOR for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

In term safety of LIFMIOR monotherapy (n=103), LIFMIOR plus methotrexate (n=294), or me hotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 years), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study, 60 patients with extended oligoarthritis (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with LIFMIOR at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and

demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued LIFMIOR therapy in patients who do not respond within 3 months of initiating LIFMIOR therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of LIFMIOR following its long-term use in patients with JIA.

## Paediatric patients with plaque psoriasis

The efficacy of LIFMIOR was assessed in a randomised, double-blind, placebo-controlled study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis (as defined by a sPGA score  $\geq$  3, involving  $\geq$  10% of the BSA, and PASI  $\geq$  12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately controlled on topical therapy.

Patients received LIFMIOR 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 week (Atweek 12, more patients randomised to LIFMIOR had positive efficacy responses (e.g. PASL75) than those randomised to placebo.

## Paediatric Plaque Psoriasis Outcomes at 12 Weeks

|                                  | LIFMIOR<br>0.8 mg/kg Onc | 2)                   |
|----------------------------------|--------------------------|----------------------|
|                                  | Weekly<br>(N = 1(b)      | Placebo<br>(N = 105) |
| PASI 75, n (%)                   | 60 (67%)                 | 12 (11%)             |
| PASI 50, n (%)                   | (759) <sup>a</sup>       | 24 (23%)             |
| sPGA "clear" or "minimal", n (%) | 56 (53%) <sup>a</sup>    | 14 (13%)             |

Abbreviation: sPGA-static Physician Global Assessment.

After the 12-week double-blind treatment period, all patients received LIFMIOR 0.8 mg/kg (up to 50 mg) once weekly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the courle-olind period.

During a randomised wither wa period, significantly more patients re-randomised to placebo experienced disease release (loss of PASI 75 response) compared with patients re-randomised to LIFMIOR. With configure therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of LIFMIOR 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyind the 48 week study discussed above. Long-term experience with LIFMIOR was generally comparable to the original 48-week study and did not reveal any new safety findings.

## Pharmacokinetic properties

Etanercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products as well as the parent compound.

## Absorption

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg LIFMIOR, the average maximum serum concentration observed in healthy volunteers was  $1.65 \pm 0.66 \,\mu\text{g/ml}$ , and the area under the curve was  $235 \pm 96.6 \,\mu\text{g} \cdot \text{hr/ml}$ .

a. p < 0.0001 compared with placebo.

Mean serum concentration profiles at steady state in treated RA patients were C<sub>max</sub> of 2.4 mg/l vs. 2.6 mg/l, C<sub>min</sub> of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg LIFMIOR once weekly (n=21) vs. 25 mg LIFMIOR twice weekly (n=16), respectively. In an openlabel, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs were 466  $\mu$ g $\bullet$ hr/ml and 474  $\mu$ g $\bullet$ hr/ml for 50 mg LIFMIOR once weekly (N = 154) and 25 mg twice weekly (N = 148), respectively.

## **Distribution**

A biexponential curve is required to describe the concentration time curve of etanercept. The contral volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

## Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hour Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower that the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of EVA fOR in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

There is no apparent pharmacokinetic difference between males and fem les

## Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

## Special populations

## Renal impairment

Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etarercept concentrations were not observed in patients with acute renal failure. The presence of recalium airment should not require a change in dosage.

## Hepatic impairment

Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

## Elderly

The impact of advanced ege was studied in the population pharmacokinetic analysis of etanercept serum concentrations. Clearance and volume estimates in patients aged 65 to 87 years were similar to estimates in patients less than 65 years of age.

## Paediatric population

## rediatric patients with juvenile idiopathic arthritis

In a polyarticular-course juvenile idiopathic arthritis trial with LIFMIOR, 69 patients (aged 4 to 17 years) were administered 0.4 mg LIFMIOR/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

## Paediatric patients with plaque psoriasis

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum

steady state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24, and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etanercept twice weekly, up to maximum dose of 50 mg per week). These mean concentrations were similar to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice weekly.

#### 5.3 Preclinical safety data

In the toxicological studies with LIFMIOR, no dose-limiting or target organ toxicity was evident. LIFMIOR was considered to be non-genotoxic from a battery of in vitro and in vivo studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with LIFMIOR due to the development of neutralising antibodies in rodents.

LIFMIOR did not induce lethality or notable signs of toxicity in mice or rats following a singl subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. LIFMIQ dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in A ommended drug concentrations that were over 27-fold higher than that obtained in humans ct.nolonger dose of 25 mg.

#### 6. PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Sucrose Sodium chloride L-Arginine hydrochloride Sodium phosphate monobasic dihydrate Sodium phosphate dibasic dihydrate Water for injections

#### 6.2 **Incompatibilities**

In the absence of compatibility his medicinal product must not be mixed with other medicinal products.

#### 6.3 Shelf life

30 months.

## autions for storage

gerator  $(2^{\circ}C - 8^{\circ}C)$ .

IOR may be stored at temperatures up to a maximum of 25°C for a single period of up to four eks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks of removal from refrigeration.

Keep the pre-filled pens in the outer carton in order to protect from light.

#### 6.5 Nature and contents of container

Pre-filled pen (MYCLIC) containing a pre-filled syringe of LIFMIOR. The syringe inside the pen is made from clear type 1 glass with a stainless steel 27 gauge needle, rubber needle cover, and plastic plunger. The needle cap of the pre-filled pen contains dry natural rubber (a derivative of latex). See section 4.4.

Cartons contain 2, 4 or 12 pre-filled pens of LIFMIOR with 2, 4 or 12 alcohol swabs. Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

## Instructions for use and handling

Before injection, LIFMIOR single-use pre-filled pens should be allowed to reach room temperature (approximately 15 to 30 minutes). The needle cover should not be removed while allowing the pre-filled pen to reach room temperature. By looking though the inspection window, the solution should be clear to slightly opalescent, colourless to pale yellow or pale brown, and may contain small translucent or white particles of protein.

Comprehensive instructions for administration are given in the package leaflet, section we bring the MYCLIC pre-filled pen to inject LIFMIOR."

Any unused product or waste material should be disposed of in accordance with a carrequirements.

## 7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1165/011 EU/1/16/1165/012 EU/1/16/1165/013

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

Date of first authorisation 13 February 2017 Date of last rene val: {Day month YYYY}

## 10. DAYÉ OF REVISION OF THE TEXT

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

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

LIFMIOR 10 mg powder and solvent for solution for injection for paediatric use.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg of etanercept. When reconstituted, the solution contains 10 mg/ml of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Eta ercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligant binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH<sub>2</sub> and CH<sub>3</sub> regions, but not the CH<sub>1</sub> region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The specific activity of etanercept is 1.7 x 10<sup>6</sup> units/mg.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (powder injection).

The powder is white. The solvent is a clear colourless liquid.

## 4. CLINICAL PARTICULAR

## 4.1 Therapeutic indication

## Juvenile idiopathic arthritis

Treatment of polyarthitis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adol scents from the age of 2 years who have had an inadequate response to, or who have proved intoler in oil method of the contraction of the contra

Treatment of proriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to or who have proved intolerant of, methotrexate.

Reaction of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inal equate response to, or who have proved intolerant of, conventional therapy.

LIFMIOR has not been studied in children aged less than 2 years.

## Paediatric plaque psoriasis

Treatment of chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

## 4.2 Posology and method of administration

LIFMIOR treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of juvenile idiopathic arthritis or paediatric plaque psoriasis. Patients treated with LIFMIOR should be given the Patient Alert Card.

## Posology

Special populations

Renal and hepatic impairment No dose adjustment is required.

## Paediatric population

The 10 mg presentation is for paediatric patients prescribed a dose of 10 mg or less Each vial of LIFMIOR 10 mg should be used on a single occasion in a single patient, and the remander of the vial should be discarded.

## Juvenile idiopathic arthritis

The recommended dose is 0.4 mg/kg (up to a maximum of 25 mg per dose given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses or 0.5 mg kg (up to a maximum of 50 mg per dose) given once weekly. Discontinuation of treatment should be considered in patients who show no response after 4 months.

No formal clinical trials have been conducted in children aged 2 to 3 years. However, limited safety data from a patient registry suggest that the safety profile in children from 2 to 3 years of age is similar to that seen in adults and children aged 4 years and offer when dosed every week with 0.8 mg/kg subcutaneously (see section 5.1).

There is generally no applicable use of LIR (IOR in children aged below 2 years in the indication juvenile idiopathic arthritis.

Paediatric plaque psoriasis (age (pars and above)

The recommended dose is 0.8 mg/k, (up to a maximum of 50 mg per dose) once weekly for up to 24 weeks. Treatment should be in a hued in patients who show no response after 12 weeks.

If re-treatment with LIEM OR is indicated, the above guidance on treatment duration should be followed. The dose should be 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly.

There is general an applicable use of LIFMIOR in children aged below 6 years in the indication plaque psories:

## Method of administration

LIFMIOL is administered by subcutaneous injection. LIFMIOR powder for solution must be expositifuted in 1 ml of solvent before use (see section 6.6).

Comprehensive instructions for the preparation and administration of the reconstituted LIFMIOR vial are given in the package leaflet, section 7, "Instructions for preparation and giving an injection of LIFMIOR."

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Sepsis or risk of sepsis.

Treatment with LIFMIOR should not be initiated in patients with active infections, including chronic or localised infections.

## 4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

## Infections

Patients should be evaluated for infections before, during, and after treatment with LIFMIOR, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range to 300 hours).

Serious infections, sepsis, tuberculosis, and opportunistic infections, including invasive fungal infections, listeriosis and legionellosis, have been reported with the use of LIFMIOR (see ection 4.8). These infections were due to bacteria, mycobacteria, fungi, viruses and parasites (including protozoa). In some cases, particular fungal and other opportunistic infections have not been recognised, resulting in delay of appropriate treatment and sometimes death. In evaluating patients for infections, the patient's risk for relevant opportunistic infections (e.g., exposure to endemic mycoses) should be considered.

Patients who develop a new infection while undergoing treatment with LENIOR should be monitored closely. Administration of LIFMIOR should be discontinued if a patient develops a serious infection. The safety and efficacy of LIFMIOR in patients with chronic infections have not been evaluated. Physicians should exercise caution when considering the use of NFMIOR in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections, such as advanced or poorly controlled diabetes.

## **Tuberculosis**

Cases of active tuberculosis, including miliary tuberculosis and tuberculosis with extra-pulmonary location, have been reported in patients treated with LIFMIOR.

Before starting treatment with LIFMIOR 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, i.e., tuberculin skin test and chest X-ray, 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's alert card. Prescribers are reminded of the risk of false negatives ube culin skin test results, especially in patients who are severely ill or immunocomprohised.

If active tubercylosis is diagnosed, LIFMIOR therapy must not be initiated. If inactive ('latent') tubercylosis is diagnosed, treatment for latent tubercylosis must be started with anti-tubercylosis therapy before the initiation of LIFMIOR, and in accordance with local recommendations. In this stuation, the benefit/risk balance of LIFMIOR therapy should be very carefully considered.

All atients 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 LIFMIOR treatment.

## Hepatitis B reactivation

Reactivation of hepatitis B in patients who were previously infected with the hepatitis B virus (HBV) and had received concomitant TNF-antagonists, including LIFMIOR, has been reported. This includes reports of reactivation of hepatitis B in patients who were anti-HBc positive but HBsAg negative. Patients should be tested for HBV infection before initiating treatment with LIFMIOR. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when administering LIFMIOR in patients

previously infected with HBV. These patients should be monitored for signs and symptoms of active HBV infection throughout therapy and for several weeks following termination of therapy. Adequate data from treating patients infected with HBV with anti-viral therapy in conjunction with TNF-antagonist therapy are not available. In patients who develop HBV infection, LIFMIOR should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

## Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving LIFMIOR. LIFMIOR should be used with caution in patients with a history of hepatitis C.

## Concurrent treatment with anakinra

Concurrent administration of LIFMIOR and anakinra has been associated with an increased risk of serious infections and neutropenia compared to LIFMIOR alone. This combination has not demonstrated increased clinical benefit. Thus, the combined use of LIFMIOR and anakinra is of recommended (see sections 4.5 and 4.8).

## Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and LIFMIOR resulted in classed incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

## Allergic reactions

Allergic reactions associated with LIFMIOR administration have been a ported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, LIFMIOR therapy should be discontinued immediately and appropriate therapy initiated.

## **Immunosuppression**

The possibility exists for TNF-antagonists, including LP MIOR, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with LIFMIOR, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cells of the conditions.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which results it in thout sequelae. Patients with a significant exposure to varicella virus should temporarily distort hue LIFMIOR therapy and be considered for prophylactic treatment with Varicella Zoster Implene Globulin.

The safety and executed LIFMIOR in patients with immunosuppression have not been evaluated.

## Malignancies a d ymphoproliferative disorders

Solid and haematopoietic malignancies (excluding skin cancers)

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been relived in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. In the postmarketing setting, cases of leukaemia have been reported in patients treated with TNF-antagonists. 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.

Based on current knowledge, a possible risk for the development of lymphomas, leukaemia or other haematopoietic or solid malignancies in patients treated with a TNF-antagonist cannot be excluded.

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

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy  $\leq$  18 years of age), including LIFMIOR, in the postmarketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies typically associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

## Skin cancers

Melanoma and non-melanoma skin cancer (NMSC) have been reported in patients treated with TNF-antagonists, including LIFMIOR. Postmarketing cases of Merkel cell carcinoma have been reported very infrequently in patients treated with LIFMIOR. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Combining the results of controlled clinical trials, more cases of NMSC were observed a patients receiving LIFMIOR compared with control patients, particularly in patients with policies.

## Vaccinations

Live vaccines should not be given concurrently with LIFMIOR. No data as available on the secondary transmission of infection by live vaccines in patients receiving LIFMIOR. In a double-blind, placebo-controlled, randomised clinical study in adult patients with psoriatic arthritis, 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study, most psoriatic arthritis patients receiving LIFMIOR were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but three in aggregate were moderately lower, and few patients had two-fold rises in titres compared to patient, not receiving LIFMIOR. The clinical significance of this is unknown.

## Autoantibody formation

Treatment with LIFMIOR may result in the formation of autoimmune antibodies (see section 4.8).

## Haematologic reactions

Rare cases of pancytopenia and tery rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with LIFMIOR. Caution should be exercised in patients being treated with LIFMIOR who have a process history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g., persistent ever, sore throat, bruising, bleeding, paleness) whilst on LIFMIOR, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, LIFMIOR should be discontinued.

## Neurological disorders

There have been rare reports of CNS demyelinating disorders in patients treated with LIFMIOR (see section 4.8). Additionally, there have been rare reports of peripheral demyelinating polyneuropathies (includin) Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy). Although no clinical trials have been performed evaluating LIFMIOR therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing LIFMIOR to patients with pre-existing or recent onset of demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

## Combination therapy

In a controlled clinical trial of two years duration in adult rheumatoid arthritis patients, the combination of LIFMIOR and methotrexate did not result in unexpected safety findings, and the safety profile of LIFMIOR when given in combination with methotrexate was similar to the profiles reported in studies of LIFMIOR and methotrexate alone. Long-term studies to assess the safety of the

combination are ongoing. The long-term safety of LIFMIOR in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

The use of LIFMIOR in combination with other systemic therapies or phototherapy for the treatment of psoriasis has not been studied.

## Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dose adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

## Congestive heart failure (Cardiac failure congestive)

Physicians should use caution when using LIFMIOR in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking LIFMIOR. There have also been rare (< 0.1%) reports of new onset CHF, including CHF in patients without known pre-existing cardiovascular diseases ones of these patients have been under 50 years of age. Two large clinical trials evaluating the discoil LIFMIOR in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening LHF in those patients assigned to LIFMIOR treatment.

## Alcoholic hepatitis

In a phase II randomised placebo-controlled study of 48 hospitalised rate not treated with LIFMIOR or placebo for moderate to severe alcoholic hepatitis, LIFMIOR was not educacious, and the mortality rate in patients treated with LIFMIOR was significantly higher after a months. Consequently, LIFMIOR should not be used in patients for the treatment of the bolic hepatitis. Physicians should use caution when using LIFMIOR in patients who also have no derate to severe alcoholic hepatitis.

## Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with LIFMIOR in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown LIFMIOR to be an effective treatment for Wegener's granulomatosis. The incidence of non-cycloped malignancies of various types was significantly higher in patients treated with LIFMIOR that in the control group. LIFMIOR is not recommended for the treatment of Wegener's granulomatoris.

## Hypoglycaemia in patients treated for diabetes

There have been reports of lypo lycaemia following initiation of LIFMIOR in patients receiving medication for diabetes, pressitating a reduction in anti-diabetic medication in some of these patients.

## Special population

## Elderly

In the Phase 3 studies in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, no overall differences in adverse events, serious adverse events, and serious infections in patients age 65 or older who ecceived LIFMIOR were observed compared with younger patients. However, caution should be earlised when treating the elderly and particular attention paid with respect to occurrence of infections.

## Paediatric population

## Vaccinations

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating LIFMIOR therapy (see Vaccinations, above).

Inflammatory bowel disease (IBD) and uveitis in patients with juvenile idiopathic arthritis (JIA) There have been reports of IBD and uveitis in JIA patients being treated with LIFMIOR (see section 4.8).

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

## Concurrent treatment with anakinra

Adult patients treated with LIFMIOR and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either LIFMIOR or anakinra alone (historical data).

In addition, in a double-blind, placebo-controlled trial in adult patients receiving background methotrexate, patients treated with LIFMIOR and anakinra were observed to have a higher rate serious infections (7%) and neutropenia than patients treated with LIFMIOR (see sections 4.4 and 4.8). The combination LIFMIOR and anakinra has not demonstrated increased clinical be efficient and is therefore not recommended.

## Concurrent treatment with abatacept

In clinical studies, concurrent administration of abatacept and LIFMIOR resulted in increased incidences of serious adverse events. This combination has not demonstrate increased clinical benefit; such use is not recommended (see section 4.4).

## Concurrent treatment with sulfasalazine

In a clinical study of adult patients who were receiving established loses of sulfasalazine, to which LIFMIOR was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison or groups treated with LIFMIOR or sulfasalazine alone. The clinical significance of this interaction is unknown. Physicians should use caution when considering combination therapy with sulfasalazine.

## Non-interactions

In clinical trials, no interactions have been observed when LIFMIOR was administered with glucocorticoids, salicylates (except sulfa arazare), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with methotrexate, digoxin or warfaria.

## 4.6 Fertility, pregnancy and lactation

## Women of childs aring totential

Women of childreaking potential should consider the use of appropriate contraception to avoid becoming pregrant during LIFMIOR therapy and for three weeks after discontinuation of therapy.

## Pregnance

Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the letts of neonatal rat due to etanercept. The effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. A higher rate of major birth defects was observed in one observational study comparing pregnancies exposed to etanercept (n=370) during the first trimester with pregnancies not exposed to etanercept or other TNF-antagonists (n=164) (adjusted odds ratio 2.4, 95% CI: 1.0-5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. In another observational multi-country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]=1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also

showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. LIFMIOR should only be used during pregnancy if clearly needed.

Etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with LIFMIOR during pregnancy. The clinical impact of this is unknown, however, infants may be at increased risk of infection. Administration of live vaccines to infants for 16 weeks after the mother's last dose of LIFMIOR is generally not recommended.

Etanercept has been reported to be excreted in human milk following subcutaneous administration. In lactating rats following subcutaneous administration, etanercept was excreted in the milk and deterred in the serum of pups. Because immunoglobulins, in common with many and it is excreted in human milks and in the serum of pups. excreted in human milk, a decision must be made whether to discontinue breast-feeding or to discontinue LIFMIOR therapy, taking into account the benefit of breast-feeding for the benefit of therapy for the woman.

## **Fertility**

Preclinical data about peri- and postnatal toxicity of etanercept and of effects of eran cept on fertility and general reproductive performance are not available.

## Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use maching n performed.

#### 4.8 **Undesirable effects**

Summary of the safety profile

Paediatric population

Undesirable effects in paediatric patients venile idiopathic arthritis In general, the adverse events in paedicts patients with juvenile idiopathic arthritis were similar in and dul patients (see below, Undesirable effects in adults). frequency and type to those seem Differences from adults and oth al considerations are discussed in the following paragraphs.

The types of infections seen in c inical trials in juvenile idiopathic arthritis patients aged 2 to 18 years erate and consistent with those commonly seen in outpatient paediatric were generally mild to populations. Severe a ver e events reported included varicella with signs and symptoms of aseptic d without sequelae (see also section 4.4), appendicitis, gastroenteritis, alty disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic it belies mellitus, and soft tissue and post-operative wound infection.

in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children d an infection while receiving LIFMIOR during 3 months of the study (part 1, open-label), frequency and severity of infections was similar in 58 patients completing 12 months of label extension therapy. The types and proportion of adverse events in juvenile idiopathic furitis patients were similar to those seen in trials of LIFMIOR in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of LIFMIOR compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

There have been reports of inflammatory bowel disease and uveitis in JIA patients being treated with LIFMIOR from post-marketing sources, including a very small number of cases indicating a positive rechallenge (see section 4.4).

Undesirable effects in paediatric patients with plaque psoriasis

In a 48-week study in 211 children aged 4 to 17 years with paediatric plaque psoriasis, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis.

## Adult population

## Undesirable effects in adults

The most commonly reported adverse reactions are injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), infections (such as upper respiratory infections bronchitis, bladder infections and skin infections), allergic reactions, development of autoantibodies itching, and fever.

Serious adverse reactions have also been reported for LIFMIOR. TNF-antagonists, such as LIFMIOR, affect the immune system and their use may affect the body's defenses against infection and cancer. Serious infections affect fewer than 1 in 100 patients treated with LIFMIOR. Report have included fatal and life-threatening infections and sepsis. Various malignancies have a so been reported with use of LIFMIOR, including cancers of the breast, lung, skin and lymph glands (lymphoma).

Serious haematological, neurological and autoimmune reactions have an obeen reported. These include rare reports of pancytopenia and very rare reports of aplicate and mia. Central and peripheral demyelinating events have been seen rarely and very rarely, respectively, with LIFMIOR use. There have been rare reports of lupus, lupus-related conditions, and valculitis.

## Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials in adults and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction) using the following categories: very common ( $\geq 1/100$ ); common ( $\geq 1/100$ ); uncommon ( $\geq 1/1000$ ); rare ( $\geq 1/10000$ ); rare ( $\geq 1/10000$ ); very rare ( $\leq 1/100000$ ); not known (cannot be stimated from the available data).

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10  | Golumo<br>1/100 to<br>110 | Uncommon<br>≥ 1/1,000 to < 1/100  | Rare<br>≥ 1/10,000 to<br>< 1/1,000   | Very Rare<br>< 1/10,000 | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|---|---------------------------|---|--|-------------------------|--|
| Infections and infestations   | in ec on<br>(inciding<br>upper<br>respiratory<br>tract<br>infection,<br>bronchitis,<br>cystitis,<br>skin<br>infection)* |                           | Serious infections<br>(including<br>pneumonia,<br>cellulitis, arthritis<br>bacterial, sepsis and<br>parasitic infection)* | Tuberculosis, opportunistic infection (including invasive fungal, protozoal, bacterial, atypical mycobacterial, viral infections, and Legionella)* |                         | Hepatitis B reactivation, listeria   |
| Neoplasms<br>benign,<br>malignant and<br>unspecified<br>(including cysts<br>and polyps) |   |                           | Non-melanoma skin cancers* (see section 4.4)  | Malignant melanoma<br>(see section 4.4),<br>lymphoma,<br>leukaemia   |                         | Merkel cell<br>carcinoma (see<br>section 4.4)                                |
| Blood and<br>lymphatic<br>system disorders  |   |                           | Thrombocytopenia,<br>anaemia,<br>leukopenia,<br>neutropenia   | Pancytopenia*  | Aplastic<br>anaemia*    | Histiocytosis<br>haematophagic<br>(macrophage<br>activation                  |

| System Organ<br>Class  | Very<br>Common<br>≥ 1/10 | Common ≥ 1/100 to < 1/10   | Uncommon<br>≥ 1/1,000 to < 1/100   | Rare<br>≥ 1/10,000 to<br>< 1/1,000  | Very Rare < 1/10,000             | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|--|--------------------------|--|--|---|----------------------------------|--|
| Immune system disorders  |                          | Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation* | Vasculitis (including anti- neutrophilic cytoplasmic antibody positive vasculitis)   | Serious<br>allergic/anaphylactic<br>reactions (including<br>angioedema,<br>bronchospasm),<br>sarcoidosis  |                                  | syndrome) <sup>†</sup> Worsening of symptoms of dermatomyositis              |
| Nervous system<br>disorders  |                          | Tormation  |  | CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions, such as optic neuritis and transverse myelitis (see section 4.4), peripheral demyelinating (vental including GANIA as Barré syntrom chronic including olyncuropathy, demyelinating olyncuropathy, demyelinating polyncuropathy, and multifocal motor neuropathy (see section 4.4), seizure | ali                              |  |
| Eye disorders Cardiac disorders  |                          |  | Uveitis, schritis  Worksning of ardiac Cilure congestive (see ection 4.4)  | New onset cardiac failure congestive (see section 4.4)  |                                  |  |
| Respiratory,<br>thoracic, and<br>mediastinal<br>disorders<br>Hepatobiliary |                          | ,00  | Elevated liver   | Interstitial lung<br>disease (including<br>pneumonitis and<br>pulmonary fibrosis)*<br>Autoimmune  |                                  |  |
| disorders Skin and subcutaneous tissue disorders                           | (a)                      | ruritus, rash  | enzymes*  Angioedema, psoriasis (including new onset or worsening and pustular, primarily palms and soles), urticaria, psoriasiform rash | hepatitis*  Stevens-Johnson syndrome, cutaneous vasculitis (including hypersensitivity vasculitis), erythema multiforme, lichenoid reactions  | Toxic<br>epidermal<br>necrolysis |  |
| Microbox selectal<br>and consective<br>beste disorders                     |                          |  |  | Cutaneous lupus<br>erythematosus,<br>subacute cutaneous<br>lupus erythematosus,<br>lupus-like syndrome  |                                  |  |

| System Organ<br>Class   | Very<br>Common<br>≥ 1/10   | Common ≥ 1/100 to < 1/10 | Uncommon<br>≥ 1/1,000 to < 1/100 | Rare<br>≥ 1/10,000 to<br>< 1/1,000 | Very Rare<br>< 1/10,000 | Frequency Not<br>Known<br>(Cannot be<br>Estimated<br>from Available<br>Data) |
|---|--|--------------------------|----------------------------------|------------------------------------|-------------------------|--|
| General<br>disorders and<br>administration<br>site conditions | Injection<br>site<br>reactions<br>(including<br>bleeding,<br>bruising,<br>erythema,<br>itching,<br>pain,<br>swelling)* | Pyrexia                  |                                  |                                    |                         | is   |

<sup>\*</sup>see Description of selected adverse reactions, below.

## Description of selected adverse reactions

## Malignancies and lymphoproliferative disorders

One hundred and twenty-nine (129) new malignancies of various types were observed rheumatoid arthritis patients treated in clinical trials with LIFMIOR for approximately 6 years, including 231 patients treated with LIFMIOR in combination with meth relate in the 2-year active-controlled study. The observed rates and incidences in these line al trials were similar to those expected for the population studied. A total of 2 malignancies ed in clinical studies of soriatic arthritis patients. In clinical approximately 2 years duration involving 240 LIFMIOR-tre studies conducted for more than 2 years with 351 ankylesin sp ndylitis patients, 6 malignancies were reported in LIFMIOR-treated patients. In a group of 2,711 haque psoriasis patients treated with LIFMIOR in double-blind and open-label studies of o 2.5 years, 30 malignancies and 43 nonmelanoma skin cancers were reported.

In a group of 7,416 patients treated with LXEMION in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical rials, 18 lymphomas were reported.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

## Injection site reactions

Compared to placebo, pair nts with rheumatic diseases treated with LIFMIOR had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the LIFMIOR treatment groups, and the majority of patients who were given treatment received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, ome patients developed recall injection site reactions characterised by a skin reaction at the most received topical preparations, such as corticosteroids, or oral antihistamines. Additionally, ome patients developed recall injection site reactions characterised by a skin reaction at the most received topical preparations, along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 13.6% of patients treated with LimMIOR developed injection site reactions compared with 3.4% of placebo-treated patients during the first 12 weeks of treatment.

## Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life-threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with LIFMIOR for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin

<sup>†</sup>Please see sub-section 'Undesirable effects in paediatric patients with juvenile idiopathic arthritis' above.

infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either LIFMIOR alone, methotrexate alone or LIFMIOR in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of LIFMIOR with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with LIFMIOR and those treated with placebo for plaque psoriasis in placebo-controlled trials of up to 24 weeks duration. Serious infections experienced by LIFMIOR-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, *Streptococcal* fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of LIFMIOR; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred wining few weeks after initiating treatment with LIFMIOR in patients who have underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). LIFMIOR treatment may increase mortality in patients with established sepsis.

Opportunistic infections have been reported in association with LIFMIQ parasitic (including protozoal), viral (including herpes zoster), bacterial liding *Listeria* and Legionella), and atypical mycobacterial infections. In a pooled data set clinical trials, the overall incidence of opportunistic infections was 0.09% for the 15,402 no received LIFMIOR. The exposure-adjusted rate was 0.06 events per 100 patient-years marketing experience. ctions worldwide were invasive approximately half of all of the case reports of opportunistic info fungal infections. The most commonly reported invasive for gal infections included Candida, Pneumocystis, Aspergillus, and Histoplasma. Invasia angal infections accounted for more than half of the fatalities amongst patients who developed histic infections. The majority of the reports with a fatal outcome were in patients with *Pneurococtis* pneumonia, unspecified systemic fungal infections, and aspergillosis (see section 4.

## Autoantibodies

for autoantibodies at multiple timepoints. Of the rheumatoid Adult patients had serum sample arthritis patients evaluated for ar an ar antibodies (ANA), the percentage of patients who developed new positive ANA (≥1:40) w er in patients treated with LIFMIOR (11%) than in placebotage of patients who developed new positive anti-double-stranded treated patients (5%). The rcei igher by radioimmunoassay (15% of patients treated with LIFMIOR DNA antibodies was also compared to 4% of pt ceb)-treated patients) and by Crithidia luciliae assay (3% of patients treated to none of placebo-treated patients). The proportion of patients treated with loped anticardiolipin antibodies was similarly increased compared to rents. The impact of long-term treatment with LIFMIOR on the development of seases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have by copied other autoantibodies in conjunction with a lupus-like syndrome or rashes that are conjunctible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

## Pancytopenia and aplastic anaemia

There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4).

## *Interstitial lung disease*

In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47%

(frequency uncommon). There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

## Concurrent treatment with anakinra

In studies when adult patients received concurrent treatment with LIFMIOR plus anakinra, a higher rate of serious infections compared to LIFMIOR alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000/mm<sup>3</sup>). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

## Elevated liver enzymes

In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double this periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enames was 4.18% (frequency common).

## Autoimmune hepatitis

In controlled clinical trials of etanercept across all indications, the frequency (incide ce proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant chethotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant ceanment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmure lapatitis was 0.24% (frequency uncommon).

## Paediatric population

See Summary of the safety profile, above.

## 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 valuese 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 dose-limiting toxicities was observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m² followed by subcutaneous doses of 16 kg/m² administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg LIFMIOR subcutaneously twice weekly for 3 weeks without experiencing und sirable effects. There is no known antidote to LIFMIOR.

## 5. PHYRMACOLOGICAL PROPERTIES

## 5.1. Pharmacodynamic properties

Phaemacotherapeutic group: Immunosuppressants, Tumour Necrosis Factor alpha (TNF-α) inhibitors, ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells, including T-cells, leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF binding to its cell surface receptors, and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs

exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors, such as etanercept, possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

## Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are independent regulated by TNF.

## Clinical efficacy and safety

This section presents data from three studies in juvenile idiopathic arthritis, one study in paediatric patients with plaque psoriasis, four studies in adults with rheumatoid arthritis, and four studies in adults with plaque psoriasis.

## Paediatric population

Paediatric patients with juvenile idiopathic arthritis

The safety and efficacy of LIFMIOR were assessed in a two part study in 69 children with polyarticular-course juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset tients aged 4 to 17 years with moderately to types (polyarthritis, pauciarthritis, systemic onset). A severely active polyarticular-course juvenile idi pathic arthritis refractory to, or intolerant of, methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal mg/kg/day or 10 mg maximum). In part 1, all patients anti-inflammatory drug and/or prednison received 0.4 mg/kg (maximum 25 mg e dose) LIFMIOR subcutaneously twice weekly. In part 2, patients with a clinical response at day 9 were randomised to remain on LIFMIOR or receive placebo for four months and assessed for dis e flare. Responses were measured using the ACR Pedi 30, defined as  $\geq 30\%$  improvement least three of six and  $\geq 30\%$  worsening in no more than one of six JRA core set criteria, including tive joint count, limitation of motion, physician and patient/parent global assessments, fund gal assessment, and erythrocyte sedimentation rate (ESR). Disease flare orsening in three of six JRA core set criteria and  $\geq 30\%$  improvement in not more than one of RA core set criteria and a minimum of two active joints. he six

In part 1 of the (trdy, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 c 25 (24%) patients remaining on LIFMIOR experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo (p=0.007). From the start of part 2, the median time to flare was 11 to days for patients who received LIFMIOR and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on LIFMIOR continued to improve from month 3 through month 7, while those who received placebo did not improve.

In an open-label, safety extension study, 58 paediatric patients from the above study (from the age of 4 years at time of enrolment) continued to receive LIFMIOR for up to 10 years. Rates of serious adverse events and serious infections did not increase with long-term exposure.

Long-term safety of LIFMIOR monotherapy (n=103), LIFMIOR plus methotrexate (n=294), or methotrexate monotherapy (n=197) were assessed for up to 3 years in a registry of 594 children aged 2 to 18 years with juvenile idiopathic arthritis, 39 of whom were 2 to 3 years of age. Overall, infections

were more commonly reported in patients treated with etanercept compared to methotrexate alone (3.8 versus 2%), and the infections associated with etanercept use were of a more severe nature.

In another open-label single-arm study, 60 patients with extended oligoarthritis (15 patients aged 2 to 4, 23 patients aged 5 to 11 and 22 patients aged 12 to 17 years old), 38 patients with enthesitis-related arthritis (12 to 17 years old), and 29 patients with psoriatic arthritis (12 to 17 years old) were treated with LIFMIOR at a dose of 0.8 mg/kg (up to a maximum of 50 mg per dose) administered weekly for 12 weeks. In each of the JIA subtypes, the majority of patients met ACR Pedi 30 criteria and demonstrated clinical improvement in secondary endpoints such as number of tender joints and physician global assessment. The safety profile was consistent with that observed in other JIA studies.

Studies have not been done in patients with juvenile idiopathic arthritis to assess the effects of continued LIFMIOR therapy in patients who do not respond within 3 months of initiating LIFMIOR therapy. Additionally, studies have not been conducted to assess the effects of discontinuing or reducing the recommended dose of LIFMIOR following its long-term use in patients with IA

## Paediatric patients with plaque psoriasis

The efficacy of LIFMIOR was assessed in a randomised, double-blind, placebo-captre led study in 211 paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasi (1s defined by an sPGA score  $\geq$  3, involving  $\geq$  10% of the BSA, and PASI  $\geq$  12). Eligible patients had a history of receiving phototherapy or systemic therapy, or were inadequately control of the topical therapy.

Patients received LIFMIOR 0.8 mg/kg (up to 50 mg) or placebo once weekly for 12 weeks. At week 12, more patients randomised to LIFMIOR had positive efficact responses (e.g., PASI 75) than those randomised to placebo.

Paediatric Plaque Psoriasis Outcomes at 12 Weeks

| ·                                | LIFMIOR   |                              |
|----------------------------------|---|------------------------------|
| <b>.</b> .                       | 0.8 mg/kg Once                                  |                              |
| X                                | Weekly  | Placebo                      |
| PASI 75, n (%)                   | $\frac{\text{(N = 106)}}{60 (57\%)^{\text{a}}}$ | $\frac{(N = 105)}{12(11\%)}$ |
| PASI 50, n (%)                   | 79 (75%) <sup>a</sup>                           | 24 (23%)                     |
| sPGA "clear" or "minimal" is (%) | 56 (53%) <sup>a</sup>                           | 14 (13%)                     |

Abbreviation: sPGA-state Physician Global Assessment

After the 12-week double-blind treatment period, all patients received LIFMIOR 0.8 mg/kg (up to 50 mg) once waskly for additional 24 weeks. Responses observed during the open-label period were similar to those observed in the double-blind period.

During a randomised withdrawal period, significantly more patients re-randomised to placebo experienced disease relapse (loss of PASI 75 response) compared with patients re-randomised to PAGOR. With continued therapy, responses were maintained up to 48 weeks.

The long-term safety and effectiveness of LIFMIOR 0.8 mg/kg (up to 50 mg) once weekly was assessed in an open-label extension study of 181 paediatric subjects with plaque psoriasis for up to 2 years beyond the 48 week study discussed above. Long-term experience with LIFMIOR was generally comparable to the original 48-week study and did not reveal any new safety findings.

## Adult patients with rheumatoid arthritis

The efficacy of LIFMIOR was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg LIFMIOR or placebo were administered subcutaneously twice a week for 6 consecutive

a. p < 0.0001 compared with placebo

months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with LIFMIOR at 3 and 6 months than in patients treated with placebo (ACR 20: LIFMIOR 62% and 59%, placebo 23% and 11% at 3 and 6 months, respectively: ACR 50: LIFMIOR 41% and 40%, placebo 8% and 5% at months 3 and 6, respectively; p<0.01 LIFMIOR vs. placebo at all timepoints for both ACR 20 and ACR 50 responses).

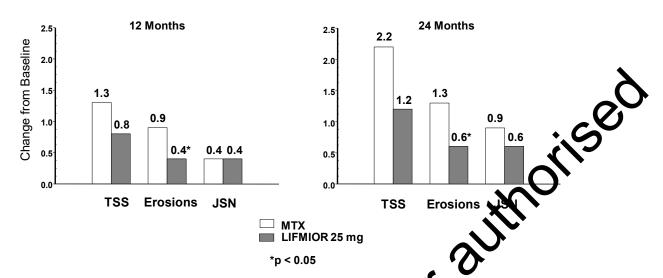
Approximately 15% of subjects who received LIFMIOR achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving LIFMIOR, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. LIFMIOR was significantly better than placebo in all components. The ACR criteria, as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (FrQ), which included disability, vitality, mental health, general health status, and arthritis-associated each status subdomains, was administered every 3 months during the trial. All subdomains of the FrAQ were improved in patients treated with LIFMIOR compared to controls at 3 and 6 morths.

After discontinuation of LIFMIOR, symptoms of arthritis generally returned within a month. Re-introduction of treatment with LIFMIOR after discontinuation of up to 34 months resulted in the same magnitudes of responses as patients who received LIFMIOR without illterruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 10 years in open-label extension treatment trials when patients received Int MoR without interruption.

The efficacy of LIFMIOR was compared to methotrexat in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had new eceived treatment with methotrexate. Doses of 10 mg or 25 mg LIFMIOR were administered subsu ene busly (SC) twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement, including onset of action within 2 weeks with LIFMIOR 25 was similar to that seen in the previous trials and was maintained for up to 24 months. At base patients had a moderate degree of disability, with mean HAO scores of 1.4 to 1.5. Treatm wit LIFMIOR 25 mg resulted in substantial improvement at 12 months, with about 44% of t chieving a normal HAO score (less than 0.5). This benefit was maintained in Year 2 of this

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) are its components, the erosion score and Joint Space Narrowing (JSN) score. Radiographs of hands/wests and feet were read at baseline and 6, 12, and 24 months. The 10 mg LIFMIOR dose had consistently less effect on structural damage than the 25 mg dose. LIFMIOR 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The difference in USS and JSN were not statistically significant between methotrexate and LIFMIOR 25 mg. The results are shown in the figure below.

## Radiographic Progression: Comparison of LIFMIOR vs. Methotrexate in Patients with RA of <3 Years Duration



In another active-controlled, double-blind, randomised study, clinical efficiency, safety, and radiographic progression in RA patients treated with LIFMIOR alone (25 m) twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and the combination of LIFMIOR and methotrexate initiated concurrently were compared in 682 adult active the unatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) (the than methotrexate.

Patients in the LIFMIOR in combination with methot, wate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement or DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single the app groups (results shown in table below). Significant advantages for LIFMIOR in combination with methotrexate compared with LIFMIOR monotherapy and methotrexate monotherapy were also observed after 24 months.

## Clinical Efficacy Results at 12 Months: Comparison of LIFMIOR vs. Methotrexate vs. LIFMIOR in Combination with Methotrexate in Patients with RA of 6 Months **To 20 Years Duration**

|                             |              |           | LIFMIOR +                             | _        |
|-----------------------------|--------------|-----------|---------------------------------------|----------|
| Endpoint                    | Methotrexate | LIFMIOR   | Methotrexate                          |          |
|                             | (n = 228)    | (n = 223) | (n = 231)                             | <u></u>  |
| A COD D                     |              |           |                                       | <b>\</b> |
| ACR Responses <sup>a</sup>  |              |           |                                       |          |
| ACR 20                      | 58.8%        | 65.5%     | 74.5% <sup>†, φ</sup>                 |          |
| ACR 50                      | 36.4%        | 43.0%     | 63.2% <sup>†,ф</sup>                  | ~()      |
| ACR 70                      | 16.7%        | 22.0%     | 39.8% <sup>†, ф</sup>                 |          |
| DAS                         |              |           |                                       |          |
| Baseline score <sup>b</sup> | 5.5          | 5.7       | 5.5                                   |          |
| Week 52 score <sup>b</sup>  | 3.0          | 3.0       | $2.3^{\dagger,\phi}$                  | •        |
| Remission <sup>c</sup>      | 14%          | 18%       | 37% <sup>†,ф</sup>                    |          |
| HAQ                         |              |           |                                       |          |
| Baseline                    | 1.7          | 1.7       | \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ |          |
| Week 52                     | 1.1          | 1.0       | $0.8^{\dagger,\phi}$                  |          |

a: Patients who did not complete 12 months in the study were considered to be nonresponders.

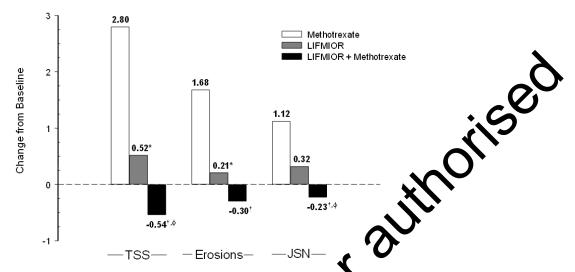
Radiographic progression at 12 months was significantly less in the LIFMIOR group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below). nat. (see fig.

b: Values for Disease Activity Score (DAS) are means.

c: Remission is defined as DAS <1.6.

Pairwise comparison p-values:  $\dagger = p < 0.05$  for comparison so s LIFMIOR + methotrexate vs. methotrexate and  $\phi = p < 0.05$  for comparisons of IIOR + methotrexate vs. LIFMIOR.

# Radiographic Progression: Comparison of LIFMIOR vs. Methotrexate vs. LIFMIOR in Combination with Methotrexate in Patients with RA of 6 Months To 20 Years Duration (12 Month Results)



Pairwise comparison p-values: \* = p < 0.05 for comparisons of LIFMIOR vs. methotrexate, † = p < 0.05 for comparisons of LIFMIOR + methotrexate vs. methotrexate and  $\phi$  = p < 0.05 for comparisons of LIFMIOR + methotrexate vs. LIFMIOR.

Significant advantages for LIFMIOR in combination with methotrexate compared with LIFMIOR monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for LIFMIOR monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dra ped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change  $\leq$  0.5) at 24 months was higher in the LIFMIOR in combination with methotrexate group compared with the LIFMIOR alone and methotrexate alone groups (62% 50%, and 36%, respectively; p<0.05). The difference between LIFMIOR alone and methotrexate alone was also significant (p<0.05). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacly of 50 mg LIFMIOR (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patient, received placebo, 214 patients received 50 mg LIFMIOR once weekly and 153 patients received 73 mg LIFMIOR twice weekly. The safety and efficacy profiles of the two LIFMIOR treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data it week 16 did not show comparability (non-inferiority) between the two regimens.

## *dua patients with plaque psoriasis*

II MIOR is recommended for use in patients as defined in section 4.1. Patients who "failed to respond to" in the target population is defined by insufficient response (PASI<50 or PGA less than good), or worsening of the disease while on treatment, and who were adequately dosed for a sufficiently long duration to assess response with at least each of the three major systemic therapies as available.

The efficacy of LIFMIOR versus other systemic therapies in patients with moderate to severe psoriasis (responsive to other systemic therapies) has not been evaluated in studies directly comparing LIFMIOR with other systemic therapies. Instead, the safety and efficacy of LIFMIOR were assessed in four randomised, double-blind, placebo-controlled studies. The primary efficacy endpoint in all four

studies was the proportion of patients in each treatment group who achieved the PASI 75 (i.e., at least a 75% improvement in the Psoriasis Area and Severity Index score from baseline) at 12 weeks.

Study 1 was a Phase 2 study in patients with active, but clinically stable, plaque psoriasis involving  $\geq 10\%$  of the body surface area who were  $\geq 18$  years old. One hundred and twelve (112) patients were randomised to receive a dose of 25 mg of LIFMIOR (n=57) or placebo (n=55) twice a week for 24 weeks.

Study 2 evaluated 652 patients with chronic plaque psoriasis using the same inclusion criteria as study 1 with the addition of a minimum psoriasis area and severity index (PASI) of 10 at screening. LIFMIOR was administered at doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week for 6 consecutive months. During the first 12 weeks of the double-blind treatment period, patients received placebo or one of the above three LIFMIOR doses. After 12 weeks of treatment patients in the placebo group began treatment with blinded LIFMIOR (25 mg twice a week): patients in the active treatment groups continued to week 24 on the dose to which they were originally randomised.

Study 3 evaluated 583 patients and had the same inclusion criteria as study 2. Patients this study received a dose of 25 mg or 50 mg LIFMIOR, or placebo twice a week for 12 weeks and then all patients received open-label 25 mg LIFMIOR twice weekly for an additions 24 weeks.

Study 4 evaluated 142 patients and had similar inclusion criteria to study 2 and 3. Patients in this study received a dose of 50 mg LIFMIOR or placebo once weekly for 11 weeks and then all patients received open-label 50 mg LIFMIOR once weekly for an additional 12 weeks.

In study 1, the LIFMIOR-treated group had a significantly ligher proportion of patients with a PASI 75 response at week 12 (30%) compared to the placebo-treated group (2%) (p<0.0001). At 24 weeks, 56% of patients in the LIFMIOR-treated group had refreshed the PASI 75 compared to 5% of placebo-treated patients. Key results of studies 2,2 and, are shown below.

Responses of Patients with Psoriasis in Studies 2, 3 and 4

|                     | Study 2    |                      |                 |          |                 | Study 3 |         |         | Study 4 |         |                    |
|---------------------|------------|----------------------|-----------------|----------|-----------------|---------|---------|---------|---------|---------|--------------------|
|                     |            | LIFMIOR              |                 |          |                 |         | LIFMIOR |         |         | LIFMIOR |                    |
|                     |            | 25 r                 | ng '            | 12       | mg              |         | 25 mg   | 50 mg   |         | 50 mg   | 50 mg              |
|                     | Placebo    | BIW                  |                 | RIW      |                 | Placebo | BIW     | BIW     | Placebo | QW      | QW                 |
|                     | n = 166    | n=                   |                 | <b>Y</b> | n =             | n = 193 | n = 196 | n = 196 | n = 46  | n = 96  | n = 90             |
|                     | wk 12      | 162                  | 162             | 164      | 164             | wk 12   | wk 24 <sup>a</sup> |
| Respons             |            | $\mathbf{v}^{\perp}$ | wk              | wk       | wk              |         |         |         |         |         |                    |
| e (%)               |            | 12                   | 24 <sup>a</sup> | 12       | 24 <sup>a</sup> |         |         |         |         |         |                    |
| PASI 50             | 14         | 58                   | 70              | 74*      | 77              | 9       | 64*     | 77*     | 9       | 69*     | 83                 |
| PASI 75             | 4          | 34*                  | 44              | 49*      | 59              | 3       | 34*     | 49*     | 2       | 38*     | 71                 |
| DSGA <sub>b</sub> , | 70         |                      |                 |          |                 |         |         |         |         |         |                    |
| clear or            | <b>\</b> ' |                      |                 |          |                 |         |         |         |         |         |                    |
| almo t              | •          |                      |                 |          |                 |         |         |         |         |         |                    |
| lear                | 5          | 34*                  | 39              | 49*      | 55              | 4       | 39*     | 57*     | 4       | 39*     | 64                 |

\*p 0.0001 compared with placebo

a. No statistical comparisons to placebo were made at week 24 in studies 2 and 4 because the original placebo group began receiving LIFMIOR 25 mg BIW or 50 mg once weekly from week 13 to week 24. b. Dermatologist Static Global Assessment. Clear or almost clear defined as 0 or 1 on a 0 to 5 scale.

Among patients with plaque psoriasis who received LIFMIOR, significant responses relative to placebo were apparent at the time of the first visit (2 weeks) and were maintained through 24 weeks of therapy.

Study 2 also had a drug withdrawal period during which patients who achieved a PASI improvement of at least 50% at week 24 had treatment stopped. Patients were observed off treatment for the

occurrence of rebound (PASI ≥150% of baseline) and for the time to relapse (defined as a loss of at least half of the improvement achieved between baseline and week 24). During the withdrawal period, symptoms of psoriasis gradually returned, with a median time to disease relapse of 3 months. No rebound flare of disease and no psoriasis-related serious adverse events were observed. There was some evidence to support a benefit of re-treatment with LIFMIOR in patients initially responding to treatment.

In study 3, the majority of patients (77%) who were initially randomised to 50 mg twice weekly and had their LIFMIOR dose decreased at week 12 to 25 mg twice weekly maintained their PASI 75 response through week 36. For patients who received 25 mg twice weekly throughout the study, the PASI 75 response continued to improve between weeks 12 and 36.

In study 4, the LIFMIOR-treated group had a higher proportion of patients with PASI 75 at week 12 (38%) compared to the placebo-treated group (2%) (p<0.0001). For patients who received 50 reg once weekly throughout the study, the efficacy responses continued to improve with 71% achie ing PASI 75 at week 24.

In long-term (up to 34 months) open-label studies where LIFMIOR was given without iterruption, clinical responses were sustained and safety was comparable to shorter-term studies.

An analysis of clinical trial data did not reveal any baseline disease characteristics that would assist clinicians in selecting the most appropriate dosing option (intermittent or collinuous). Consequently, the choice of intermittent or continuous therapy should be based up in physician judgment and individual patient needs.

## Antibodies to LIFMIOR

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical esponse or adverse events.

In subjects treated with approved doses of canercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, 9.7% of subjects with psoriasis, and 4.8% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoliasis statects.

In a long-term repliasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of aktibodies observed at each assessment point was up to approximately 9%.

## 592 Pharmacokinetic properties

Eta ercept serum values were determined by an Enzyme-Linked Immunosorbent Assay (ELISA) method, which may detect ELISA-reactive degradation products as well as the parent compound.

## Special populations

## Renal impairment

Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal failure. The presence of renal impairment should not require a change in dosage.

## Hepatic impairment

Increased etanercept concentrations were not observed in patients with acute hepatic failure. The presence of hepatic impairment should not require a change in dosage.

## Paediatric population

## Paediatric patients with juvenile idiopathic arthritis

In a polyarticular-course juvenile idiopathic arthritis trial with LIFMIOR, 69 patients (aged 4 to 17 years) were administered 0.4 mg LIFMIOR/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

## Paediatric patients with plaque psoriasis

Patients with paediatric plaque psoriasis (aged 4 to 17 years) were administered 0.8 mg/kg (up to a maximum dose of 50 mg per week) of etanercept once weekly for up to 48 weeks. The mean serum steady-state trough concentrations ranged from 1.6 to 2.1 mcg/ml at weeks 12, 24 and 48. These mean concentrations in patients with paediatric plaque psoriasis were similar to the concentrations observed in patients with juvenile idiopathic arthritis (treated with 0.4 mg/kg etan respective weekly, up to maximum dose of 50 mg per week). These mean concentrations were surellal to those seen in adult patients with plaque psoriasis treated with 25 mg etanercept twice-weekly.

## Adults

## Absorption

Etanercept is slowly absorbed from the site of subcular ous injection, reaching maximum concentration approximately 48 hours after a sing The absolute bioavailability is 76%. With tate concentrations are approximately twice as high twice-weekly doses, it is anticipated that steady as those observed after single doses. After single subcutaneous dose of 25 mg LIFMIOR, the average maximum serum concentration observed in heathy volunteers was  $1.65 \pm 0.66 \,\mu g/ml$ , and the area Mean serum concentration profiles at steady state in treated under the curve was  $235 \pm 96.6 \,\mu \text{g} \cdot \text{hr} \cdot \text{m}$ RA patients were C<sub>max</sub> of 2.4 mg/lvs 2. mg/l,  $C_{min}$  of 1.2 mg/l vs. 1.4 mg/l, and partial AUC of 297 mgh/l vs. 316 mgh/l for 50 mg FMIOR once weekly (n=21) vs. 25 mg LIFMIOR twice weekly (i), single-dose, two-treatment, crossover study in healthy (n=16), respectively. In an o volunteers, etanercept admir ed as a single 50 mg/ml injection was found to be bioequivalent to of 25 mg/ml. two simultaneous injeg

In a population pharmackinetics analysis in ankylosing spondylitis patients, the etanercept steady state AUCs with 46%  $\mu$ g•hr/ml and 474  $\mu$ g•hr/ml for 50 mg LIFMIOR once weekly (N= 154) and 25 mg twice weekly (N = 148), respectively.

## Distribution

A hiexponential curve is required to describe the concentration time curve of etanercept. The central curve of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l.

## Elimination

Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of LIFMIOR in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar. There is no apparent pharmacokinetic difference between males and females.

Linearity

Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

### 5.3 Preclinical safety data

In the toxicological studies with LIFMIOR, no dose-limiting or target organ toxicity was evident. LIFMIOR was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with LIFMIOR due to the development of neutralising antibodies in rodents.

LIFMIOR did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. LIFMIOR did not envious dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-to see serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

### 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Powder

Mannitol (E421)

Sucrose

Trometamol

Solvent

Water for injections

### 6.2 Incompatibilities

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

### 6.3 Shelf life

3 years.

From a microbial ogical point of view, the reconstituted medicinal product should be used immediately. Elemical and physical in-use stability has been demonstrated for 6 hours at temperatures not above 25° C after reconstitution.

### 64 Special precautions for storage

Sto in a refrigerator (2°C - 8°C). Do not freeze.

LIFMIOR may be stored at temperatures up to a maximum of 25° C for a single period of up to four weeks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks of removal from refrigeration.

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

### 6.5 Nature and contents of container

Clear glass vial (4 ml, type I glass) with rubber stopper, aluminium seal, and flip-off plastic cap. LIFMIOR is supplied with pre-filled syringes containing water for injection. The syringes are type I glass.

Cartons contain 4 vials of LIFMIOR, 4 pre-filled syringes of water for injections, 4 needles, 4 vial adaptors and 8 alcohol swabs.

### 6.6 Special precautions for disposal and other handling

### <u>Instructions</u> for use and handling

LIFMIOR is reconstituted with 1 ml water for injections before use, and administered by subcutage us injection. The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes or particles. Some white foam may remain in the vial – this is normal. LIFMIOR scale not be used if all the powder in the vial is not dissolved within 10 minutes. Start again with another vial.

Comprehensive instructions for the preparation and administration of the reconstitute LIFMIOR vial are given in the package leaflet, section 7, "Instructions for preparation and giving a injection of LIFMIOR"

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

### 7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium

### 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1165/001

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

Date of first authorisation: 13 February 2017 Date of last represent (DD month YYYY)

### 10. DATE OF REVISION OF THE TEXT

Leta led information on this medicinal product is available on the website of the European Medicines Agracy http://www.ema.europa.eu.

All Activities of Authorities of Aut

### ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS 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 DECEMBER 11 THE MEDICINAL PRODUCT

### A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Boehringer Ingelheim Pharma KG Birkendorfer Strasse 65 D-88397 Biberach an der Riss Germany

Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin Dublin 22 Ireland

yer authorised Name and address of the manufacturers responsible for batch release

Wyeth Pharmaceuticals

New Lane

Havant

Hampshire, PO9 2NG

United Kingdom

Pfizer Manufacturing Belgium NV

Rijksweg 12,

**2870 Puurs** 

Belgium

The printed package leaflet of the medicinal product st state the name and address of the manufacturer responsible for the release of the

### В. CONDITIONS OR RESTRICT **EGARDING SUPPLY AND USE**

Medicinal product subject to res dical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

### C. AND REQUIREMENTS OF THE MARKETING

### y Update Reports

ts for submission of periodic safety update reports for this medicinal product are set of Union reference dates (EURD list) provided for under Article 107c(7) of Directive and any subsequent updates published on the European medicines web-portal.

### CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

### Risk Management Plan (RMP)

The 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

Patient Alert Card which is to be given to patients using LIFMIOR.

The healthcare professional's educational material should contain the following key elements:

• Teaching guide to facilitate training of the patients in the safe use of the pre-filled by the pre-filled by the pre-filled by the pre-filled by the patients in the safe use of the pre-filled by the pre-filled by the patients in the safe use of the pre-filled by the pre-filled b

- Instructional materials to share with patients

Medicinal product. The Patient's Alert Card should contain the following key elements for patients treated LIFMIOR:

ANNEX III
LABELLING AND PACENCE PEAFLET

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### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON TEXT -** EU/1/16/1165/002-004

### 1. NAME OF THE MEDICINAL PRODUCT

LIFMIOR 25 mg powder and solvent for solution for injection etanercept

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of LIFMIOR contains 25 mg etanercept.

### 3. LIST OF EXCIPIENTS

The other ingredients in LIFMIOR are:

Powder: Mannitol, sucrose and trometamol.

Solvent: Water for injections

### 4. PHARMACEUTICAL FORM AND CONTENT

Powder and solvent for solution for injection

- 4 vials of powder
- 4 pre-filled syringes of 1 ml solvent
- 4 stainless steel injection needles
- 4 vial adaptors
- 8 alcohol swabs

8 vials of powder

8 pre-filled syringes of 1 all selvent

8 stainless steel injection needless

8 vial adaptors

16 alcohol swabs

24 vials of www.

24 pre-fill d syringes of 1 ml solvent

24 strinless steel injection needles

May 1 agantors

40 alcohol swabs

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

| Kee                  | p out of the sight and reach of children.   |
|----------------------|---|
| 7.                   | OTHER SPECIAL WARNING(S), IF NECESSARY  |
| 8.                   | EXPIRY DATE   |
|                      |   |
| EXF                  | ,,0   |
| 9.                   | SPECIAL STORAGE CONDITIONS  |
| Stor                 | e in a refrigerator.  |
|                      | not freeze.   |
| Refe                 | er to package leaflet for alternative storage details.  |
| Afte                 | or preparing the LIFMIOR solution, immediate use is recommended up to a maximum of 6 hou  |
| 10.                  | SPECIAL PRECAUTIONS FOR DISPOSAL OF INJSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
| 11.                  | NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER  |
| Pfize<br>Bou<br>1050 | er Europe MA EEIG<br>levard de la Plaine 17<br>) Bruxelles<br>gium  |
| 12.                  | MARKET NG ANTHORISATION NUMBER(S)   |
| EU/<br>EU/<br>EU/    | 1/16/1/65/002<br>1/16/1/65/003<br>1/16/1/65/004   |
| W                    | BATCH NUMBER  |
|                      |   |

### 15. INSTRUCTIONS ON USE

### INFORMATION IN BRAILLE

# Medicinal product no longer authorised

**TEXT FOR VIAL LABEL** – EU/1/16/1165/002-004

## To the state of th NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LIFMIOR 25 mg powder for injection etanercept Subcutaneous use

### 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

### 3. **EXPIRY DATE**

**EXP** 

### **BATCH NUMBER** 4.

Lot

## Nedicinal production of the second section of the se CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

**TEXT FOR SYRINGE LABEL** – EU/1/16/1165/002-004

### NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for LIFMIOR Subcutaneous use

### 2. METHOD OF ADMINISTRATION

## CONTENTS BY WEIGHT, BY VOLUMEOR BY UNIT 1 ml water for injections 6. OTHER

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON TEXT – (25 mg Pre-filled Syringe) –** EU/1/16/1165/005-007

### NAME OF THE MEDICINAL PRODUCT

LIFMIOR 25 mg solution for injection in pre-filled syringe etanercept

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe of LIFMIOR contains 25 mg etanercept.

### LIST OF EXCIPIENTS 3.

The other ingredients in LIFMIOR are:

Revobasic dihydrate, sodium Sucrose, sodium chloride, L-arginine hydrochloride, sodium phospha phosphate dibasic dihydrate and water for injections.

### PHARMACEUTICAL FORM AND

Solution for injection in pre-filled syringe

4 pre-filled syringes

4 alcohol swabs

8 pre-filled syringes

8 alcohol swabs

24 pre-filled syringes

24 alcohol swabs

### **SOUTE(S) OF ADMINISTRATION**

eaflet before use. Read the

e solution after it has reached room temperature (15 to 30 minutes after taking the product the refrigerator).

nject slowly, at an angle of 45° to 90° to the skin.

### 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   |
| Ctono       | in a nafri annatan   |
|             | in a refrigerator. of freeze.  |
|             | to package leaflet for alternative storage details.  |
| rcoror      | to puckage rearies for anomalive storage details.  |
| Keep        | the pre-filled syringes in the outer carton in order to protect from light.  |
|             |  |
| 10.         | SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUC  |
| 10.         | OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, II  |
|             | APPROPRIATE  |
|             | 70   |
|             | <b>~</b> O)  |
| 11.         | NAME AND ADDRESS OF THE MARKETING ACTION HOLDER  |
|             | NO.  |
|             | Europe MA EEIG   |
|             | evard de la Plaine 17  |
|             | Bruxelles  |
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| 12.         | MARKETING AUTHORISANON NUMBER(S)   |
|             | XV.  |
|             | /16/1165/005   |
|             | /16/1165/006   |
| EU/I        | /16/1165/007   |
| 13.         | BATCH NUMPEL   |
| 10.         |  |
| Lot         |  |
|             |  |
| 4.4         | The state of the s |
| 14.         | GENERAL CLASSIFICATION FOR SUPPLY  |
| 11          |  |
| <b>し</b>    | •  |
| <u>-</u>    | INSTRUCTIONS ON USE  |
| <b>1</b> 3. | INDIROCIIONO UN UDE  |

### 16. INFORMATION IN BRAILLE

LIFMIOR 25 mg

Medicinal product no longer authorised

TEXT FOR PRE-FILLED SYRINGE LABEL - (25 mg Pre-filled Syringe) - EU/1/16/1165/005-- authorised 007

### NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LIFMIOR 25 mg injection etanercept Subcutaneous use

### METHOD OF ADMINISTRATION 2.

Read the package leaflet before use.

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT 25 mg/0.5 ml 6. OTHER

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON TEXT – (50 mg Pre-filled Syringe)** – EU/1/16/1165/008-010

### NAME OF THE MEDICINAL PRODUCT

LIFMIOR 50 mg solution for injection in pre-filled syringe etanercept

### STATEMENT OF ACTIVE SUBSTANCE(S) 2.

Each pre-filled syringe of LIFMIOR contains 50 mg etanercept.

### 3. LIST OF EXCIPIENTS

Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate dibasic dihydrate and water for injections.

### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe

2 pre-filled syringes2 alcohol swabs

- 4 pre-filled syringes
- 4 alcohol swabs
- 12 pre-filled syringes
- 12 alcohol swabs

### **METHOD AN** TE(S) OF ADMINISTRATION

Read the packag eaflet efore use.

Subcutaneous

on after it has reached room temperature (15 to 30 minutes after taking the product efrigerator).

lowly, at an angle of  $45^{\circ}$  to  $90^{\circ}$  to the skin.

### 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 | e in a refrigerator.   |
|       | ot freeze.   |
| Refe  | r to package leaflet for alternative storage details.  |
| Keep  | the pre-filled syringes 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 AD |
| D۳    | E MA FFIG  |
|       | er Europe MA EEIG evard de la Plaine 17  |
|       | Bruxelles  |
| Belg  | ium  |
| 12.   | MARKETING AUTHORISA VOX NUMBER(S)  |
| EU/1  | ./16/1165/008  |
|       | /16/1165/009   |
| EU/1  | ./16/1165/010  |
| 13.   | BATCH NYMBER   |
| Lot   | cillia.  |
| 14.   | CENERAL CLASSIFICATION FOR SUPPLY  |
| Ö     |  |
| 15.   | INSTRUCTIONS ON USE  |
| 15.   | INSTRUCTIONS ON USE  |

### INFORMATION IN BRAILLE 16.

LIFMIOR 50 mg

Medicinal product no longer authorised

TEXT FOR PRE-FILLED SYRINGE – (50 mg Pre-filled Syringe) – EU/1/16/1165/008-010

## The state of the s NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LIFMIOR 50 mg injection etanercept Subcutaneous use

### 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

### 3. **EXPIRY DATE**

**EXP** 

### **BATCH NUMBER** 4.

Lot

## Medicinal Problems And American Problems And CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON TEXT – (50 mg Pre-filled Pen)** – EU/1/16/1165/011-013

### 1. NAME OF THE MEDICINAL PRODUCT

LIFMIOR 50 mg solution for injection in pre-filled pen etanercept

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen of LIFMIOR contains 50 mg etanercept.

### 3. LIST OF EXCIPIENTS

The other ingredients in LIFMIOR are:

Sucrose, sodium chloride, L-arginine hydrochloride, sodium phosphate no locasic dihydrate, sodium phosphate dibasic dihydrate and water for injections.

### 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen (MYCLIC)

- 2 MYCLIC pre-filled pens
- 2 alcohol swabs
- 4 MYCLIC pre-filled pens
- 4 alcohol swabs
- 12 MYCLIC pre-filled pens
- 12 alcohol swabs

### 5. METHOD AND POUTE(S) OF ADMINISTRATION

Read the packag Neaflet before use.

Subcutane

Injection advice:

Inject the solution after it has reached room temperature (15 to 30 minutes after taking the product from the refrigerator).

### 5. 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.  |
|       | ot freeze.  |
| Refe  | to package leaflet for alternative storage details.   |
| Keep  | the pre-filled pens 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 |
| Boul  | NAME AND ADDRESS OF THE MARKETING AN NORISATION HOLDER  r Europe MA EEIG evard de la Plaine 17 Bruxelles um                           |
| 12.   | MARKETING AUTHORISANO NUMBER(S)   |
| EU/1  | /16/1165/011<br>/16/1165/012<br>/16/1165/013  |
| 13.   | BATCH NYMBER  |
| Lot   | inia  |
| 3     | CNERAL CLASSIFICATION FOR SUPPLY  |
| 15.   | INSTRUCTIONS ON USE   |

### 16. INFORMATION IN BRAILLE

LIFMIOR 50 mg

Medicinal product no longer authorised

**TEXT FOR PRE-FILLED PEN – (50 mg Pre-filled Pen)** – EU/1/16/1165/011-013

## Thorised Tho NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LIFMIOR 50 mg solution for injection in pre-filled pen etanercept Subcutaneous use

### 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

### 3. **EXPIRY DATE**

**EXP** 

## CONTENTS BY WEIGHT, BY VOLUTE

### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON TEXT (For paediatric use)** – EU/1/16/1165/001

### NAME OF THE MEDICINAL PRODUCT

A LIFMIOR are:

...ol, sucrose and trometamol.

...ater for injections

PHARMACEUTICAL FORM AND CONTENTS

r and solvent for solution for injection

of powder

ed syringes of 1 ml solvent
s steel injection needles
ptors

wabs LIFMIOR 10 mg powder and solvent for solution for injection for paediatric use etanercept

### 2.

Each vial of LIFMIOR contains 10 mg etanercept.

### 3.

The other ingredients in LIFMIOR are: Powder: Mannitol, sucrose and trometamol.

Solvent: Water for injections

### 4.

Powder and solvent for solution for injection

- 4 vials of powder
- 4 pre-filled syringes of 1 ml solvent
- 4 stainless steel injection needles
- 4 vial adaptors
- 8 alcohol swabs

### OF ADMINISTRATION METHOD AND RO

Read the package leaf re use.

Subcutaneous us

children prescribed a dose of 10 mg or less. Follow the directions given by the The 10 mg via

d be used for just one dose in one patient, and any remaining solution should be

### 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   |
|  | EATINI DATE   |
| EXP  |   |
| 9.   | SPECIAL STORAGE CONDITIONS  |
| Store  | in a refrigerator.  |
|  | ot freeze.  |
| Refe   | r to package leaflet for alternative storage details.   |
| Afteı  | preparing the LIFMIOR solution, immediate use is recommended (up to a maximum of 6 hours).  |
| 10.  | SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MENICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE |
|  |   |
| 11.  | NAME AND ADDRESS OF THE MARKETING ALP HORISATION HOLDER   |
| Pfize  | r Europe MA EEIG  |
| Pfize<br>Boul                                | r Europe MA EEIG<br>evard de la Plaine 17   |
| Pfize<br>Boul<br>1050                        | r Europe MA EEIG<br>evard de la Plaine 17<br>Bruxelles  |
| Pfize<br>Boul                                | r Europe MA EEIG<br>evard de la Plaine 17<br>Bruxelles  |
| Pfize<br>Boul<br>1050<br>Belg                | r Europe MA EEIG<br>evard de la Plaine 17<br>Bruxelles  |
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| Pfize<br>Boul<br>1050<br>Belg<br>12.         | r Europe MA EEIG evard de la Plaine 17 Bruxelles ium  MARKETING AUTHONS TION NUMBER(S)  /16/1165/001                                  |
| Pfize<br>Boul<br>1050<br>Belg<br>12.<br>EU/1 | r Europe MA EEIG evard de la Plaine 17 Bruxelles ium  MARKETING AUTHON SATI ON NUMBER(S)  /16/1165/001  BATCH NUMBER                  |

### 16. INFORMATION IN BRAILLE

LIFMIOR 10 mg

Medicinal product no longer authorised

TEXT FOR VIAL LABEL – (For paediatric use) – EU/1/16/1165/001

## To the state of th NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

LIFMIOR 10 mg powder for injection etanercept Subcutaneous use

### 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

### 3. **EXPIRY DATE**

**EXP** 

### **BATCH NUMBER** 4.

Lot

## Medicinal product CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

TEXT FOR SYRINGE LABEL – (For paediatric use) – EU/1/16/1165/001

## NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for LIFMIOR Subcutaneous use

### 2. METHOD OF ADMINISTRATION

## CONTENTS BY WEIGHT, BY VOLUMEOR BY UNIT 1 ml water for injections 6. OTHER

B. PACKAGE LEAFLEN OF AUTHORISE OF AUTHORISE

### Package Leaflet: Information for the User

### LIFMIOR 25 mg powder and solvent for solution for injection Etanercept

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

### Read all (both sides) 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 Alert Card, which contains important safety information that you need to be aware of before and during treatment with LIFMIOR.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it in hothers. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

Information in this leaflet is organised under the following 7 set tions.

- 1. What LIFMIOR is and what it is used for
- 2. What you need to know before you use LIFMIOR
- 3. How to use LIFMIOR
- 4. Possible side effects
- 5. How to store LIFMIOR
- 6. Contents of the pack and other information
- 7. Instructions for preparing and giving an injection of LIFMIOR (See overleaf)

### 1. What LIFMIOR is and what is used for

LIFMIOR is a medicine that it hade from two human proteins. It blocks the activity of another protein in the body that cause in Cammation. LIFMIOR works by reducing the inflammation associated with certain diseases.

In adults (age logid over), LIFMIOR can be used for moderate or severe rheumatoid arthritis, psoriatic arthritis, severe axial spondyloarthritis including ankylosing spondylitis, and moderate or severe psoriasis – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For neumatoid arthritis, LIFMIOR is usually used in combination with methotrexate, although it may be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, LIFMIOR can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, LIFMIOR can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), LIFMIOR can slow down the structural damage to those joints caused by the disease.

LIFMIOR is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
  - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them evere psoriasis in patients from the age of 6 years who have had an inadequate responsato or re unable to take) phototherapies or other systemic therapies. • Severe psoriasis in patients from the age of 6 years who have had an inadequate reare unable to take) phototherapies or other systemic therapies.

### 2. What you need to know before you use LIFMIOR

### Do not use LIFMIOR

- if you, or the child you are caring for, are allergic to etanercept of the other ingredients of LIFMIOR (listed in section 6). If you or the child experience c reactions such as chest tightness, wheezing, dizziness or rash, do not inject more IFMO, and contact your doctor immediately.
- if you or the child have, or are at risk of developing us blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child, have an infection of any kild. If you are not sure, please talk to your doctor.

### Warnings and precautions

Talk to your doctor before taking LIFM OR

- Allergic reactions: If you ath fild experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more LIFMIOR, and contact your doctor immediately.
- Infections/surgery: If you or the child develop a new infection, or are about to have any major surgery, your docto mawish to monitor the treatment with LIFMIOR.
- ell your doctor if you or the child have a history of recurrent infections or or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you levelop symptoms of an infection such as fever, chills or cough, notify your doctor Y. Your doctor may decide to continue to monitor you or the child for the presence of ons after you or the child stop using LIFMIOR.
  - **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with LIFMIOR, ur doctor will check for signs and symptoms of tuberculosis before starting LIFMIOR. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Alert Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- Hepatitis B: Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with LIFMIOR. Treatment with LIFMIOR may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using LIFMIOR.

- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with LIFMIOR in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of LIFMIOR.
- Nervous system and eye disorders: Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if LIFMIOR is an appropriate treatment.
- Congestive heart failure: Tell your doctor if you or the child have a history of congestive heart failure, because LIFMIOR needs to be used with caution under these circumstances.
- Cancer: Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) of any other cancer before you are given LIFMIOR.
  - Patients with severe rheumatoid arthritis, who have had the disease for a long time, may higher than average risk of developing lymphoma.
  - Children and adults taking LIFMIOR may have an increased risk of developing Virohoma or another cancer.
  - Some children and teenage patients who have received LIFMIOR or other in themes that work the same way as LIFMIOR have developed cancers, including unusual type. Which sometimes resulted in death.
  - Some patients receiving LIFMIOR have developed skin cancers. To your doctor if you or the child develop any change in the appearance of the skin or growths in the skin.
- Chickenpox: Tell your doctor if you or the child are exposed to chickenpox when using LIFMIOR. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- **Alcohol abuse**: LIFMIOR should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- Wegener's granulomatosis: LIFMIOR is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- Anti-diabetic medicines: Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you or the child need less anti-diabetic medicine while taking LIFMIOR.

### Children and adolescents

- Vaccinations: If possible, children should be up to date with all vaccinations before using LIFMIOR. Some vaccine, such as oral polio vaccine, should not be given while using LIFMIOR. Please consult your doctor before you or the child receive any vaccines.
- Inflammatory by rel disease (IBD): There have been cases of IBD in patients with juvenile idiopathic at britis (IIA) treated with LIFMIOR. Tell the doctor if the child develops any abdomital camps and pain, diarrhoea, weight loss or blood in the stool.

LIFMICR should not normally be used in children with polyarthritis or extended oligoarthritis below the age of 3 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years or in children with psoriasis below the age of 6 years.

### **Wher medicines and LIFMIOR**

Tell the doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use LIFMIOR with medicines that contain the active substance anakinra or abatacept.

### Pregnancy and breast-feeding

LIFMIOR should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received LIFMIOR during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received LIFMIOR in pregnancy, compared with mothers who had not received LIFMIOR or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received LIFMIOR in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby. It is important that you tell the baby's doctors and other healthcare professionals about the use of LIFMIOR during pregnancy before the baby receives any vaccine (for more information see section 2, "Vaccinations").

Women using LIFMIOR should not breast-feed, since LIFMIOR passes into human breast hilk

### Driving and using machines

The use of LIFMIOR is not expected to affect the ability to drive or use machines

### 3. How to use LIFMIOR

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of LIFMIOR is too strong weak, talk to your doctor or pharmacist.

### Dosing for adult patients (aged 18 years or over)

Rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject LIFMIOR.

### Plaque psoriasis

The usual dose is 25 kg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once a week.

Your doc or will decide how long you should take LIFMIOR and whether retreatment is needed based on your 1 sponse. If LIFMIOR has no effect on your condition after 12 weeks, your doctor may tell you o stop taking this medicine.

### Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of LIFMIOR per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of LIFMIOR per kg bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of LIFMIOR per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If LIFMIOR has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

### Method and route of administration

LIFMIOR is administered by an injection under the skin (by subcutaneous injection).

LIFMIOR can be taken with or without food or drink.

The powder must be dissolved before use. **Detailed instructions on how to prepare and inject LIFMIOR are provided in section 7, "Instructions for preparing and giving an injection of LIFMIOR"**. Do not mix the LIFMIOR solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week LXMOR should be used.

### If you use more LIFMIOR than you should

If you have used more LIFMIOR than you should (either by injecting to putch on a single occasion or by using it too frequently), talk to a doctor or pharmacist immediately. A ways have the outer carton of the medicine with you, even if it is empty.

### If you forget to inject LIFMIOR

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed lose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

### If you stop using LIFMIOR

Your symptoms may return upon discon inuation.

If you have any further questions or the use of this medicine, ask your doctor or pharmacist.

### 4. Possible side effect

Like all medicines, his medicine can cause side effects, although not everybody gets them.

### Allergic reactions

If any of the following happen, do not inject more LIFMIOR. Tell your doctor immediately, or go to be assualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to LIFMIOR, so you should seek immediate medical attention.

### **Serious side effects**

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of **nerve disorders**, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of heart failure or worsening heart failure, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night-time shortness of breath or coughing, bluish colour of the nails or the lips
- Signs of cancers: Cancers may affect any part of the body including the skin and blood and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lun os or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that may harm form) tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking rensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent red., fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as pain, fever, reclass or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or isome casualty department at your nearest hospital.

The known side effects of LIFMIOR include the following in groups of decreasing frequency:

- Very common (may affect more than 1 in 10 people):

  Infections (including colds, sinusitist conchitis, urinary tract infections and skin infections); injection site reactions (including bleeting, bruising, redness, itching, pain, and swelling).

  Reactions at the injection site (these do not occur as often after the first month of treatment). Some patients have developed a faction at an injection site that was used before.
- Common (may affect up to 1 in 10 people):
  Allergic reactions; every rash; itching; antibodies directed against normal tissue (autoantibody formation).
- Uncommon (may affect up to 1 in 100 people):

  Serious in certions (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives
  - devated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common).
- Rare (may affect up to 1 in 1,000 people):

  Serious allergic reactions (including severe localised swelling of the skin and wheezing);
  lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow);
  melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count;
  nervous system disorders (with severe muscle weakness and signs and symptoms similar to
  those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord);
  tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome

(symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon).

- Very rare (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.
- Not known (frequency cannot be estimated from the available data): Merkel cell carcino at type of skin cancer); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); we tenn g of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

### Side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents a similar to those described above.

### Reporting of side effects

If you get any side effects, talk to your doctor or pharma ist. 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 belp provide more information on the safety of this medicine.

### 5. How to store LIFMIOR

Keep this medicine out of the sight and much of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator  $(2^{\circ}) - 8^{\circ}$ C). Do not freeze.

Before preparing the LIFMIOR solution, LIFMIOR may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks after removal from the lattigerator. It is recommended that you record the date that LIFMIOR is removed from the refrigerator and the date after which LIFMIOR should be discarded (no more than 4 weeks following the noval from the refrigerator).

After preparing the LIFMIOR solution, immediate use is recommended. However, the solution may be used for up to 6 hours when stored at temperatures of up to 25°C.

Do not use this medicine if you notice the solution is not clear or contains particles. The solution should be clear, colourless to pale yellow or pale brown, with no lumps or flakes or particles.

Carefully dispose of any LIFMIOR solution that has not been injected within 6 hours.

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 LIFMIOR contains

The active substance in LIFMIOR is etanercept. Each vial of LIFMIOR 25 mg contains 25 mg of etanercept.

The other ingredients are:

Powder: Mannitol (E421), sucrose and trometamol

Solvent: Water for injections

### What LIFMIOR looks like and contents of the pack

LIFMIOR 25 mg is supplied as a white powder and solvent for solution for injection (powder for injection). Each pack contains 4, 8 or 24 single dose vials, 4, 8 or 24 pre-filled syringes of water for injections, 4, 8 or 24 needles, 4, 8 or 24 vial adaptors and 8, 16 or 48 alcohol swabs. Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

### Marketing Authorisation Holder:

Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium

### Manufacturer:

Wyeth Pharmaceuticals New Lane Havant Hampshire, PO9 2NG United Kingdom Niz r Manufacturing Belgium NV

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For any information about this nedicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

### 7. Instructions for preparing and giving an injection of LIFMIOR

This section is divided into the following subsections:

- a. Introduction
- b. Setting up for an injection
- c. Preparing the LIFMIOR dose for injection
- d. Adding solvent
- e. Withdrawing the LIFMIOR solution from the vial
- f. Placing the needle on the syringe
- g. Choosing an injection site
- h. Preparing the injection site and injecting the LIFMIOR solution
- i. Disposing of supplies

### a. Introduction

The following instructions explain how to prepare and inject LIFMIOR. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or bit the assistant on the techniques of self-injection or on giving an injection to a child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

This injection should not be mixed with any other medicine.

### b. Setting up for an injection

- Wash your hands thoroughly.
- Select a clean well-lit, flat working surface.
- The dose tray should contain the items lister be ow. (If not, don't use the dose tray and consult your pharmacist). Use only the items listed. **Do NOT** use any other syringe.
  - 1 LIFMIOR vial
  - 1 Pre-filled syringe containing char, colourless solvent (water for injections)
  - 1 Needle
  - 1 Vial adaptor
  - 2 Alcohol swabs
- Inspect the expiry dates on both the vial label and the syringe label. They should not be used after the month and year shown.

### c. Preparing the LUCATION dose for injection

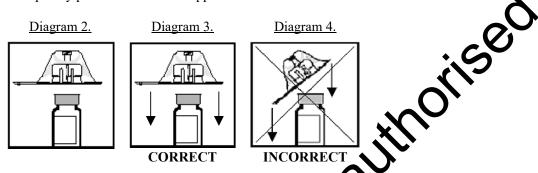
- Remove the contexts of the tray
- Remove the plastic cap from the LIFMIOR vial (see Diagram 1). **Do NOT** remove the grey stopper of cluminium ring around the top of the vial.



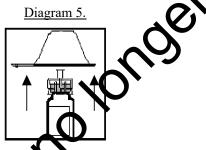


- Use a new alcohol swab to clean the grey stopper on the LIFMIOR vial. After cleaning, do not touch the stopper with your hands or allow it to touch any surface.
- Place the vial upright on a clean, flat surface.
- Remove the paper backing from the vial adaptor package.

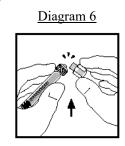
- While still in the plastic package, place the vial adaptor on top of the LIFMIOR vial so that the vial adaptor spike is centered within the raised circle on top of the vial stopper (see Diagram 2).
- Hold the vial firmly on the flat surface with one hand. With the other hand, push STRAIGHT DOWN FIRMLY on the adaptor package until you feel the adaptor spike penetrate the vial stopper and FEEL AND HEAR THE ADAPTOR RIM LOCK INTO PLACE (see Diagram 3). Do NOT push down the adaptor at an angle (see Diagram 4). It is important that the vial adaptor spike completely penetrates the vial stopper.



• While holding the vial in one hand, remove the plastic packaging from the in adaptor (see Diagram 5).



• Remove the protective cover from the syringe tip by breaking the white cap along the perforation. This is done by holding the collar of the white cap while grasping the end of the white cap with the other hand and per ling it down and then up until it is broken (see Diagram 6). Do NOT remove the white collar that remains on the syringe.



Do not use the syringe if this perforation is already broken. Start again with another dose tray. Holding the glass barrel of the syringe (not the white collar) in one hand, and the vial adaptor (not the vial) in the other, connect the syringe to the vial adaptor by inserting the tip into the opening and turn clockwise until completely secured (see Diagram 7).

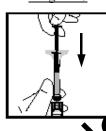
### Diagram 7



### d. Adding solvent

- While holding the vial upright on the flat surface, push the plunger VERY SLOWLY until a the solvent is in the vial. This will help to reduce foaming (lots of bubbles) (see Diagram 8).
- Once the solvent is added to the LIFMIOR, the plunger may move up by itself. This is the to air pressure and should not be of concern.





• With the syringe still attached, gently move the vial in circles a few times, to dissolve the powder (see Diagram 9). **Do NOT** shake the man Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes, or particles. Some white foam may remain in the vial this is normal. **Do NOT** use LIFMIOR if all the powder in the vial is not dissolved within 10 minutes. Start again

with another dose tray.

Diagram 9



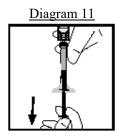
e. Withdrawing the LIFMIOR solution from the vial

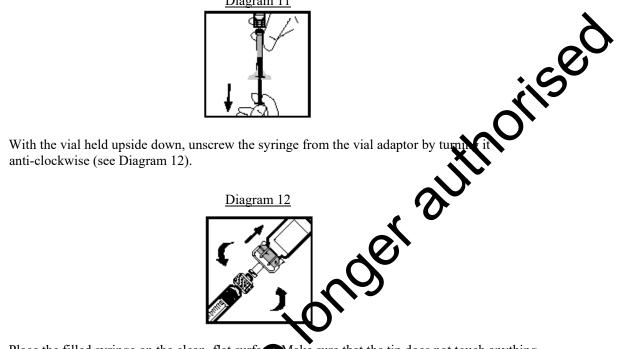
With the syringe still attached to the vial and vial adaptor, hold the vial upside down at eye level. Push the plunger all the way into the syringe (see Diagram 10).

Diagram 10



Then, slowly pull the plunger back to draw the liquid into the syringe (see Diagram 11). For adult patients, withdraw the entire volume. For children, remove only the portion of liquid as directed by your child's doctor. After you have withdrawn the LIFMIOR from the vial, you may have some air in the syringe. Do not be concerned, as you will remove the air in a later step.

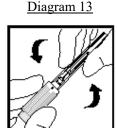




Place the filled syringe on the clean, flat surfa Make sure that the tip does not touch anything. Be careful not to push down on the plung

(Note: After you have completed these ste a small amount of liquid may remain in the vial. This is normal.)

- f. Placing the needle on the
- The needle has been p a plastic container to keep it sterile.
- er, hold the short, wide end in one hand. Place your other hand on the To open the plastic longer portion o ontainer.
- To break the se nd the larger end down and then up until broken (see Diagram 13).



- Once the seal has been broken, remove the short, wide end of the plastic container.
- The needle will remain in the long part of the package.
- While holding the needle and container in one hand, pick up the syringe and insert the syringe tip into the needle opening.
- Attach the syringe to the needle by turning it clockwise until completely secured (see Diagram 14).



Remove the needle cover by firmly pulling it straight off the syringe taking care not to touch the needle or allow the needle to touch any surfaces (see Diagram 15). Be careful not to benden twist the cover during removal to avoid damage to the needle.

Diagram 15

Vhile holding the syringe upright, remove any air bubble at its removal (s. Diagram 15).

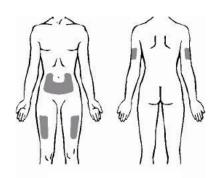


While holding the syringe upright, remove any air bubble, by slow until the air is removed (see Diagram 16).



- g. Choosing an injection
- The three recommo ed injection sites for LIFMIOR include: (1) the front of the middle thighs; bept for the 5 cm area right around the navel; and (3) the outer area of the (2) the abdomer ee Diagram 17). If you are self injecting, you should not use the outer area of the upper arms

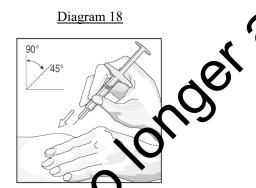
Diagram 17



- A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. **Do NOT** inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
- If you or the child have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

### h. Preparing the injection site and injecting the LIFMIOR solution

- Wipe the site where LIFMIOR is to be injected with an alcohol swab, using a circular motion.
   Do NOT touch this area again before giving the injection.
- When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
- With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90° (see Diagram 18). With experience, you will find the angle that is most confortable for you or the child. Be careful not to push the needle into the skin too slowly, or with great force.



• When the needle is completely inserted into the skin, release the skin that you are holding. With your free hand, hold the syringe near he base to stabilise it. Then push the plunger to inject all of the solution at a **slow**, steady rate (see Diagram 19).



When the syringe is empty, remove the needle from the skin; being careful to keep it at the same angle it was when it was inserted.

Press a cotton ball over the injection site for 10 seconds. Slight bleeding may occur. **Do NOT** rub the injection site. A bandage is optional.

### i. Disposing of supplies

The syringe and needles should **NEVER** be re-used. Dispose of the needles and syringe as instructed by your doctor, nurse or pharmacist.

Medicinal product no longer authorised

### Package leaflet: information for the user

### LIFMIOR 25 mg solution for injection in pre-filled syringe LIFMIOR 50 mg solution for injection in pre-filled syringe Etanercept

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

## Read all (both sides) 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 Alert Card, which contains important safety in follow hon that you need to be aware of before and during treatment with LIFMIOR.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass to not others. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

Information in this leaflet is organised under the following Tsections

- 1. What LIFMIOR is and what it is used for
- 2. What you need to know before you use LIFM OR
- 3. How to use LIFMIOR
- 4. Possible side effects
- 5. How to store LIFMIOR
- 6. Contents of the pack and other information
- 7. Instructions for preparing and giving an injection of LIFMIOR (See overleaf)

### 1. What LIFMIOR is and what it is used for

LIFMIOR is a medicine classis made from two human proteins. It blocks the activity of another protein in the body that causes in flammation. LIFMIOR works by reducing the inflammation associated with certain diseases.

In adults (rg d Sand over), LIFMIOR can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis**, and moderate or see fee **psoriasis** – in each case usually when other widely used treatments have not worked well that get or are not suitable for you.

rheumatoid arthritis, LIFMIOR is usually used in combination with methotrexate, although it may also be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, LIFMIOR can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, LIFMIOR can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), LIFMIOR can slow down the structural damage to those joints caused by the disease.

LIFMIOR is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
  - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them evere psoriasis in patients from the age of 6 years who have had an inadequate responsato or re unable to take) phototherapies or other systemic therapies. • Severe psoriasis in patients from the age of 6 years who have had an inadequate reare unable to take) phototherapies or other systemic therapies.

### 2. What you need to know before you use LIFMIOR

### Do not use LIFMIOR

- if you, or the child you are caring for, are allergic to etanercept of the other ingredients of LIFMIOR (listed in section 6). If you or the child experience c reactions such as chest tightness, wheezing, dizziness or rash, do not inject more IFMEX, and contact your doctor immediately.
- if you or the child have, or are at risk of developing us blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an infection of any kind. If you are not sure, please talk to your doctor.

### Warning and precautions

Talk to your doctor before taking LIFM OR

- Allergic reactions: If you ath fild experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more LIFMIOR, and contact your doctor immediately.
- Infections/surgery: If you or the child develop a new infection, or are about to have any major surgery, your docto mawish to monitor the treatment with LIFMIOR.
- sell your doctor if you or the child have a history of recurrent infections or or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you levelop symptoms of an infection such as fever, chills or cough, notify your doctor Y. Your doctor may decide to continue to monitor you or the child for the presence of ons after you or the child stop using LIFMIOR.
  - **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with LIFMIOR, ur doctor will check for signs and symptoms of tuberculosis before starting LIFMIOR. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Alert Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- Hepatitis B: Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with LIFMIOR. Treatment with LIFMIOR may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using LIFMIOR.

- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with LIFMIOR in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of LIFMIOR.
- Nervous system and eye disorders: Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if LIFMIOR is an appropriate treatment.
- Congestive heart failure: Tell your doctor if you or the child have a history of congestive heart failure, because LIFMIOR needs to be used with caution under these circumstances.
- Cancer: Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) of any other cancer before you are given LIFMIOR.
  - Patients with severe rheumatoid arthritis, who have had the disease for a long time, may higher than average risk of developing lymphoma.
  - Children and adults taking LIFMIOR may have an increased risk of developing Vinohoma or another cancer.
  - Some children and teenage patients who have received LIFMIOR or other in themes that work the same way as LIFMIOR have developed cancers, including unusual type. Which sometimes resulted in death.
  - Some patients receiving LIFMIOR have developed skin cancers. To your doctor if you or the child develop any change in the appearance of the skin or growths in the skin.
- Chickenpox: Tell your doctor if you or the child are exposed to chickenpox when using LIFMIOR. Your doctor will determine if preventive treatment for chickenpox is appropriate.
- Latex: The needle cover is made from latex (dry natural unber). Contact your doctor before using LIFMIOR if the needle cover will be handled by a LIFMIOR will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- Alcohol abuse: LIFMIOR should not be used for he treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the child in your care have a history of alcohol abuse.
- Wegener's granulomatosis: LIFMIOR is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- Anti-diabetic medicines: Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your octor may decide if you or the child need less anti-diabetic medicine while taking LII MICR.

### Children and adolescen

- Vaccinations: Recasible, children should be up to date with all vaccinations before using LIFMIOR. Some vaccines, such as oral polio vaccine, should not be given while using LIFMICR release consult your doctor before you or the child receive any vaccines.
- Infl. m. varory bowel disease (IBD): There have been cases of IBD in patients with juvenile ideap thic arthritis (JIA) treated with LIFMIOR. Tell the doctor if the child develops any abdominal cramps and pain, diarrhoea, weight loss or blood in the stool.

Lh WIOR should not normally be used in children with polyarthritis or extended oligoarthritis below age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

### Other medicines and LIFMIOR

Tell the doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use LIFMIOR with medicines that contain the active substance anakinra or abatacept.

### Pregnancy and breast-feeding

LIFMIOR should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received LIFMIOR during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received LIFMIOR in pregnancy, compared with mothers who had not received LIFMIOR or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received LIFMIOR in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby. It is important that you tell the baby's doctors and other healthcare professionals about the use of LIFMIOR during pregnancy before the baby receives any vaccine (for more information see section 2, "Vaccinations").

Women using LIFMIOR should not breast-feed, since LIFMIOR passes into human breast milk.

### **Driving and using machines**

The use of LIFMIOR is not expected to affect the ability to drive or use an chines.

### 3. How to use LIFMIOR

Always use this medicine exactly as the doctor has told you Ch ck with the doctor or pharmacist if you are not sure.

If you feel that the effect of LIFMIOR is too strong at too weak, talk to your doctor or pharmacist.

The pre-filled syringe is available in dose sengths of 25 mg and 50 mg.

### Dosing for adult patients (aged 18 years of over)

Rheumatoid arthritis, psoriatic a unitis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject LIFMIOR.

### Plaque psoriasis

The usual dose is 13 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week of 50 mg once a week.

You doctor will decide how long you should take LIFMIOR and whether retreatment is needed based on your response. If LIFMIOR has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

### Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of LIFMIOR (10 mg, 25 mg or 50 mg).

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of LIFMIOR per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of LIFMIOR per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of LIFMIOR per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If LIFMIOR has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

### Method and route of administration

LIFMIOR is administered by an injection under the skin (by subcutaneous injection).

LIFMIOR can be taken with or without food or drink.

Detailed instructions on how to inject LIFMIOR are provided in section 7, "Last Letions for preparing and giving an injection of LIFMIOR". Do not mix the LIFMIOR solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day (s of the week LIFMIOR should be used.

### If you use more LIFMIOR than you should

If you have used more LIFMIOR than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharm cost immediately. Always have the outer carton of the medicine with you, even if it is empty.

### If you forget to inject LIFMIOR

If you forget a dose, you should injectit as so on as you remember, unless the next scheduled dose is the next day; in which case you should sup the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

## If you stop using LIFMINE

Your symptoms hay return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

### Allergic reactions

If any of the following happen, do not inject more LIFMIOR. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet

- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to LIFMIOR, so you should seek immediate medical attention.

### **Serious side effects**

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of nerve disorders, such as numbness or tingling, changes in vision, eye pain or easet of weakness in an arm or leg
- Signs of heart failure or worsening heart failure, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdoment, light-time shortness of breath or coughing, bluish colour of the nails or the lips
- Signs of cancers: Cancers may affect any part of the body including the skin and blood, and possible signs will depend on the type and location of the cancer. These signs may include weight loss, fever, swelling (with or without pain), persistent of the presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are mide that may harm normal tissues in the body) such as pain, itching, weakness, and abnormal reathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such a pain, fever, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor in mediately, or visit the casualty department at your nearest hospital.

The known side effects of LIFM OR include the following in groups of decreasing frequency:

- Very common (ms.) affect more than 1 in 10 people):
  Infections (including volds, sinusitis, bronchitis, urinary tract infections and skin infections); injection after reactions (including bleeding, bruising, redness, itching, pain, and swelling).
  Reactions at the injection site (these do not occur as often after the first month of treatment). Some patients have developed a reaction at an injection site that was used before.
- Cynnon (may affect up to 1 in 10 people):
- Allegic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody function).

**Uncommon** (may affect up to 1 in 100 people):

Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common).

- Rare (may affect up to 1 in 1,000 people):

  Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is
- Very rare (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.
- Not known (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cancer); excessive activation of white blood cells assert tel with inflammation (macrophage activation syndrome); recurrence of hepatitis B (asliter infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash).

### Side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

### Reporting of side effects

uncommon).

If you get any side effects, talk to your dector of pharmacist. This includes any possible side effects not listed in this leaflet. You can also report ide effects directly via the national reporting system listed in <u>Appendix V</u>. By reporting Side effects you can help provide more information on the safety of this medicine.

### 5. How to store LIFWOR

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 carton and pre-filled syringe after EXP. The exply date refers to the last day of that month.

Store in a refrigerator  $(2^{\circ} - 8^{\circ}C)$ . Do not freeze.

Keep the pre-filled syringes in the outer carton in order to protect from light.

After taking a syringe from the refrigerator, wait approximately 15-30 minutes to allow the LIFMIOR solution in the syringe to reach room temperature. Do not warm in any other way. Immediate use is then recommended.

LIFMIOR may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that LIFMIOR is removed from the refrigerator and the date after which LIFMIOR should be discarded (no more than 4 weeks following the removal from the refrigerator).

Inspect the solution in the syringe. It should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for LIFMIOR. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

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 LIFMIOR contains

### 25 mg solution for injection in pre-filled syringe

The active substance in LIFMIOR is etanercept. Each pre-filled syringe contains ( providing 25 mg of etanercept.

### 50 mg solution for injection in pre-filled syringe

The active substance in LIFMIOR is etanercept. Each pre-filled syringe 1.0 ml of solution, providing 50 mg of etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine h de, sodium phosphate monobasic dihydrate and sodium phosphate dibasic dihydra ater for injections.

### What LIFMIOR looks like and contents of the pack

### 25 mg solution for injection in pre-filled syringe

LIFMIOR is supplied as a pre-filled syringe containing a clear, colourless to pale yellow or pale brown, solution for injection (solution for triection). Each pack contains 4, 8 or 24 pre-filled syringes and 4, 8 or 24 alcohol swabs. Not all page may be marketed.

### 50 mg solution for injection in pa

inge containing a clear, colourless to pale yellow or pale LIFMIOR is supplied as a pre-f h for injection). Each pack contains 2, 4 or 12 pre-filled syringes brown, solution for injection and 2, 4 or 12 alcohol sw all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site:

http://www.ema.europa.eu

7. Instructions for preparing and giving an injection of LIFMIOR

This section is divided into the following subsections:

Introduction
Step 1: Setting up for an injection
Step 2: Choosing an injection site
Step 3: Injecting the LIFMIOR solution
Step 4: Disposing of supplies

ntroduction

### Introduction

The following instructions explain how to prepare and neet LIFMIOR. Please read the instructions carefully and follow them step by step. You will be ructed by your doctor or his/her assistant on ection to a child. Do not attempt to administer an the techniques of self-injection or on giving an in injection until you are sure that you understand how to prepare and give the injection.

The LIFMIOR solution should not b with any other medicine before use.

## Step 1: Setting up for an injection

- orking surface.
- 2. Take the LIFMIO ton containing the pre-filled syringes out of the refrigerator and place it on Starting from one of the top corners, pull back the paper cover from the top tray. Remove one pre-filled syringe and one alcohol swab and place them on the o not shake the pre-filled syringe of LIFMIOR. Fold the paper cover back over the ace the carton containing any remaining pre-filled syringes back into the refrigerator. e section 5 for instructions on how to store LIFMIOR. If you have any questions about contact your doctor, nurse, or pharmacist for further instructions.
- ou should allow 15 to 30 minutes for the LIFMIOR solution in the syringe to reach room temperature. Do NOT remove the needle cover while allowing it to reach room temperature. Waiting until the solution reaches room temperature may make the injection more comfortable for you. Do not warm LIFMIOR in any other way (for example, do not warm it in a microwave or in hot water).
- 4. Assemble the additional supplies you will need for your injection. These include the alcohol swab from the LIFMIOR carton and a cotton ball or gauze.
- 5. Wash your hands with soap and warm water.

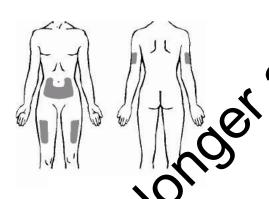
6. Inspect the solution in the syringe. It should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for LIFMIOR. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

### Step 2: Choosing an injection site

Injection sites for LIFMIOR using a pre-filled syringe include: (1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right around the navel; and (3) the outer area of the upper arms (see Diagram 1). If you are self injecting, you should not use the outer area of the upper arms.

Diagram 1 1. The three recommended injection sites for LIFMIOR using a pre-filled syringe include: (1) the





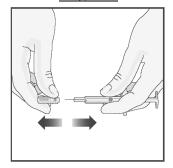
- 2. A different site should be used for each new injection. Each new injection should be given at least 3 cm from an old site. Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It helpful to keep notes on the location of the previous injections.)
- 3. If you or the child have psoriasis, yo try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skir

### Step 3: Injecting the LIFMIO

- Wipe the site where L FMTOR is to be injected with the alcohol swab, using a circular motion. **Do** NOT touch this a gain before giving the injection.
- 2. Pick up the filled syringe from the flat work surface. Remove the needle cover by firmly ht off the syringe (see Diagram 2). Be careful not to bend or twist the cover al to avoid damage to the needle.

remove the needle cover, there may be a drop of liquid at the end of the needle; this is I. Do not touch the needle or allow it to touch any surface. Do not touch or bump the unger. Doing so could cause the liquid to leak out.

### Diagram 2



- 3. When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.
  4. With a quick, short motion, push the needle all the way into the skin of 90° (see Diagram 3). With experience von with a the child. Be careful. the child. Be careful not to push the needle into the skin too slowly, or with gr

Diagram 3



5. When the needle is completely inserted nto the skin, release the skin that you are holding. With your free hand, hold the syringe near its b to stabilise it. Then push the plunger to inject all of the solution at a slow, steady rate Dagram 4).

Diagram 4



When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site for 10 seconds. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

### **Step 4: Disposing of supplies**

The pre-filled syringe is for single-use administration only. The syringe and needle should **NEVER** be re-used. **NEVER** re-cap a needle. Dispose of the needle and syringe as instructed by your doctor, nurse or pharmacist.

If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with LIFMIOR.

Medicinal product no longer authorised

### Package Leaflet: Information for the User

## LIFMIOR 50 mg solution for injection in pre-filled pen Etanercept

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

## Read all (both sides) 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 Alert Card, which contains important safety information that you need to be aware of before and during treatment with LIFMIOR.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or a child in your care. Do not pass it in hothers. It may harm them, even if their signs of illness are the same as yours or those of the child you are caring for.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### What is in this leaflet

Information in this leaflet is organised under the following 7 sections

- 1. What LIFMIOR is and what it is used for
- 2. What you need to know before you use LIFMIOR
- 3. How to use LIFMIOR
- 4. Possible side effects
- How to store LIFMIOR
- 6. Contents of the pack and other information
- 7. Using the MYCLIC pre-filled per to inject LIFMIOR (See overleaf)

### 1. What LIFMIOR is and what is used for

LIFMIOR is a medicine that it had from two human proteins. It blocks the activity of another protein in the body that cause in a mation. LIFMIOR works by reducing the inflammation associated with certain diseases.

In adults (age lo and over), LIFMIOR can be used for moderate or severe **rheumatoid arthritis**, **psoriatic arthritis**, severe **axial spondyloarthritis** including **ankylosing spondylitis**, and moderate or severe **psoriasis** – in each case usually when other widely used treatments have not worked well enough or are not suitable for you.

For neumatoid arthritis, LIFMIOR is usually used in combination with methotrexate, although it may be used alone if treatment with methotrexate is unsuitable for you. Whether used alone or in combination with methotrexate, LIFMIOR can slow down the damage to your joints caused by the rheumatoid arthritis and improve your ability to do normal daily activities.

For psoriatic arthritis patients with multiple joint involvement, LIFMIOR can improve your ability to do normal daily activities. For patients with multiple symmetrical painful or swollen joints (e.g., hands, wrists and feet), LIFMIOR can slow down the structural damage to those joints caused by the disease.

LIFMIOR is also prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
  - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them

  Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

### 2. What you need to know before you use LIFMIOR

### Do not use LIFMIOR

- if you, or the child you are caring for, are allergic to etanercept of the other ingredients of LIFMIOR (listed in section 6). If you or the child experience ic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more IFMEX, and contact your doctor immediately.
- if you or the child have, or are at risk of developing us blood infection called sepsis. If you are not sure, please contact your doctor.
- if you or the child have an infection of any kind. If you are not sure, please talk to your doctor.

### Warnings and precautions

Talk to your doctor before taking LIFM OR:

- Allergic reactions: If you ath fild experience allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more LIFMIOR, and contact your doctor immediately.
- Infections/surgery: If you or the child develop a new infection, or are about to have any major surgery, your docto mawish to monitor the treatment with LIFMIOR.
- sell your doctor if you or the child have a history of recurrent infections or or other conditions that increase the risk of infection.
- **Infections/monitoring:** Tell your doctor of any recent travel outside the European region. If you levelop symptoms of an infection such as fever, chills or cough, notify your doctor Y. Your doctor may decide to continue to monitor you or the child for the presence of ons after you or the child stop using LIFMIOR.
  - **Tuberculosis:** As cases of tuberculosis have been reported in patients treated with LIFMIOR, ur doctor will check for signs and symptoms of tuberculosis before starting LIFMIOR. This may include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Alert Card. It is very important that you tell your doctor if you or the child have ever had tuberculosis, or have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- Hepatitis B: Tell your doctor if you or the child have or have ever had hepatitis B. Your doctor should test for the presence of hepatitis B infection before you or the child begin treatment with LIFMIOR. Treatment with LIFMIOR may result in reactivation of hepatitis B in patients who have previously been infected with the hepatitis B virus. If this occurs, you should stop using LIFMIOR.

- **Hepatitis C:** Tell your doctor if you or the child have hepatitis C. Your doctor may wish to monitor the treatment with LIFMIOR in case the infection worsens.
- **Blood disorders:** Seek medical advice immediately if you or the child have any signs or symptoms such as persistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of LIFMIOR.
- Nervous system and eye disorders: Tell your doctor if you or the child have multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if LIFMIOR is an appropriate treatment.
- Congestive heart failure: Tell your doctor if you or the child have a history of congestive heart failure, because LIFMIOR needs to be used with caution under these circumstances.
- Cancer: Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) of any other cancer before you are given LIFMIOR.
  - Patients with severe rheumatoid arthritis, who have had the disease for a long time, may higher than average risk of developing lymphoma.
  - Children and adults taking LIFMIOR may have an increased risk of developing Vinohoma or another cancer.
  - Some children and teenage patients who have received LIFMIOR or other in themes that work the same way as LIFMIOR have developed cancers, including unusual type. Which sometimes resulted in death.
  - Some patients receiving LIFMIOR have developed skin cancers. To your doctor if you or the child develop any change in the appearance of the skin or growths in the skin.
- Chickenpox: Tell your doctor if you or the child are exposed to chickenpox when using LIFMIOR. Your doctor will determine if preventive treather for chickenpox is appropriate.
- Latex: The needle cap of the MYCLIC pen is made from latex (dry natural rubber). Contact your doctor before using LIFMIOR if the needle cap will be handled by, or LIFMIOR will be given to, someone with a known or possible hypersensitivity (allergy) to latex.
- **Alcohol abuse**: LIFMIOR should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if you or the children your care have a history of alcohol abuse.
- Wegener's granulomatosis: LIFMIOR is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If you or the child in your care have Wegener's granulomatosis, talk to your doctor.
- Anti-diabetic medicines: Tell your doctor if you or the child have diabetes or are taking medicines to treat diabetes. Your octor may decide if you or the child need less anti-diabetic medicine while taking LIRMICR.

### Children and adolescen

- Vaccinations: Recasible, children should be up to date with all vaccinations before using LIFMIOR. Some vaccines, such as oral polio vaccine, should not be given while using LIFMICR release consult your doctor before you or the child receive any vaccines.
- Infl. m. varory bowel disease (IBD): There have been cases of IBD in patients with juvenile ideap thic arthritis (JIA) treated with LIFMIOR. Tell the doctor if the child develops any abdominal cramps and pain, diarrhoea, weight loss or blood in the stool.

Lh WIOR should not normally be used in children with polyarthritis or extended oligoarthritis below age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of 6 years.

### Other medicines and LIFMIOR

Tell the doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines (including anakinra, abatacept or sulfasalazine), even those not prescribed by the doctor. You or the child should not use LIFMIOR with medicines that contain the active substance anakinra or abatacept.

### Pregnancy and breast-feeding

LIFMIOR should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received LIFMIOR during pregnancy, your baby may have a higher risk of getting an infection. In addition, one study found more birth defects when the mother had received LIFMIOR in pregnancy, compared with mothers who had not received LIFMIOR or other similar medicines (TNF-antagonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received LIFMIOR in pregnancy. Your doctor will help you to decide whether the benefits of treatment outweigh the potential risk to your baby. It is important that you tell the baby's doctors and other healthcare professionals about the use of LIFMIOR during pregnancy before the baby receives any vaccine (for more information see section 2, "Vaccinations").

Women using LIFMIOR should not breast-feed, since LIFMIOR passes into human breast hilk

### **Driving and using machines**

The use of LIFMIOR is not expected to affect the ability to drive or use machines.

### 3. How to use LIFMIOR

Always use this medicine exactly as your doctor has told you. Check with your doctor if or pharmacist you are not sure.

If you feel that the effect of LIFMIOR is too strong weak, talk to your doctor or pharmacist.

You have been prescribed a 50 mg strength of NFMOR. A 25 mg strength of LIFMIOR is available for doses of 25 mg.

### Dosing for adult patients (aged 18 years of over)

Rheumatoid arthritis, psoriatic a divitis, and axial spondyloarthritis including ankylosing spondylitis

The usual dose is 25 mg given twice a week or 50 mg once a week as an injection under the skin. However, your doctor may determine an alternative frequency at which to inject LIFMIOR.

### Plaque psoriasis

The usual dose is 13 mg twice a week or 50 mg once a week.

Alternatively, 50 mg may be given twice a week for up to 12 weeks, followed by 25 mg twice a week of 50 mg once a week.

You doctor will decide how long you should take LIFMIOR and whether retreatment is needed based on your response. If LIFMIOR has no effect on your condition after 12 weeks, your doctor may tell you to stop taking this medicine.

### Use in children and adolescents

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. Your doctor will determine the correct dose for the child and will prescribe an appropriate strength of LIFMIOR (10 mg, 25 mg or 50 mg).

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or enthesitis-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.4 mg of LIFMIOR per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of LIFMIOR per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 mg of LIFMIOR per kg bodyweight (up to a maximum of 50 mg), and should be given once weekly. If LIFMIOR has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

### Method and route of administration

LIFMIOR is administered by an injection under the skin (by subcutaneous injection).

LIFMIOR can be taken with or without food or drink.

Detailed instructions on how to inject LIFMIOR are provided in section 7, "Exting the MYCLIC pre-filled pen to inject LIFMIOR". Do not mix the LIFMIOR solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week LIFMIOR should be used.

### If you use more LIFMIOR than you should

If you have used more LIFMIOR than you should (either by injecting too much on a single occasion or by using it too frequently), talk to a doctor or pharmacist in mediately. Always have the outer carton of the medicine with you, even if it is empty.

### If you forget to inject LIFMIOR

If you forget a dose, you should inject it assor as you remember, unless the next scheduled dose is the next day; in which case you should sain the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

### If you stop using LIFMI

Your symptoms may etuin upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### 4. Possible side effects

ike an medicines, this medicine can cause side effects, although not everybody gets them.

### Anergic reactions

If any of the following happen, do not inject more LIFMIOR. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

- Trouble swallowing or breathing
- Swelling of the face, throat, hands, or feet
- Feeling nervous or anxious, throbbing sensations, sudden reddening of the skin and/or a warm feeling
- Severe rash, itching, or hives (elevated patches of red or pale skin that often itch)

Serious allergic reactions are rare. However, any of the above symptoms may indicate an allergic reaction to LIFMIOR, so you should seek immediate medical attention.

### **Serious side effects**

If you notice any of the following, you or the child may need urgent medical attention.

- Signs of **serious infections**, such as high fever that may be accompanied by cough, shortness of breath, chills, weakness, or a hot, red, tender, sore area on the skin or joints
- Signs of **blood disorders**, such as bleeding, bruising, or paleness
- Signs of nerve disorders, such as numbness or tingling, changes in vision, eye pain, or onse of weakness in an arm or leg
- Signs of heart failure or worsening heart failure, such as fatigue or shortness of breath with activity, swelling in the ankles, a feeling of fullness in the neck or abdomen, night time shortness of breath or coughing, bluish colour of the nails or the lips
- Signs of cancers: Cancers may affect any part of the body including the skin and lood, and possible signs will depend on the type and location of the cancer. These sign may include weight loss, fever, swelling (with or without pain), persistent cough, presence of lumps or growths on the skin
- Signs of **autoimmune reactions** (where antibodies are made that my harm normal tissues in the body) such as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- Signs of lupus or lupus-like syndrome, such as weight changes, pasistent rash, fever, joint or muscle pain, or fatigue
- Signs of **inflammation of the blood vessels** such as rain, fewer, redness or warmth of the skin, or itching.

These are rare or uncommon side effects, but are se fous conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or visit the casualty department at your nearest hospital.

The known side effects of LIFMIOR include the following in groups of decreasing frequency:

- Very common (may affect note than 1 in 10 people):
  Infections (including colds, situatis, bronchitis, urinary tract infections and skin infections);
  injection site reaction (including bleeding, bruising, redness, itching, pain, and swelling).
  Reactions at the injection site (these do not occur as often after the first month of treatment).
  Some patients have developed a reaction at an injection site that was used before.
- Common (a ay affect up to 1 in 10 people):
  Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).
  - Uncommon (may affect up to 1 in 100 people):

    lious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hives (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common).
- Rare (may affect up to 1 in 1,000 people): Serious allergic reactions (including severe localised swelling of the skin and wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the blood and bone marrow);

melanoma (a type of skin cancer); combined low platelet, red, and white blood cell count; nervous system disorders (with severe muscle weakness and signs and symptoms similar to those of multiple sclerosis or inflammation of the nerves of the eyes or spinal cord); tuberculosis; new onset congestive heart failure; seizures; lupus or lupus-like syndrome (symptoms may include persistent rash, fever, joint pain, and tiredness); skin rash, which may lead to severe blistering and peeling of the skin; lichenoid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autoimmune hepatitis; in patients also receiving methotrexate treatment, the frequency is uncommon); immune disorder that can affect the lungs, skin and lymph nodes (sarcoidosis); inflammation or scarring of the lungs (in patients also receiving methotrexate treatment, the frequency of inflammation or scarring of the lungs is uncommon).

- Very rare (may affect up to 1 in 10,000 people): failure of the bone marrow to produce crucial blood cells.
- Not known (frequency cannot be estimated from the available data): Merkel cell arcinoma (a type of skin cancer); excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weaknest with an accompanying skin rash).

### Side effects in children and adolescents

The side effects and their frequencies seen in children and adolescents are similar to those described above.

### Reporting of side effects

If you get any side effects, talk to your doctor of pharmacist. 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 <u>Appendix V</u>. By reporting side effects you can help provide more information on the safety of this medicine.

### 5. How to store LIFMIQA

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 carton and on the MYCLIC pre-filled pen star EXP. The expiry date refers to the last day of that month.

Store in a efficient or  $(2^{\circ} - 8^{\circ}C)$ . Do not freeze.

Keep the pre-filled pens in the outer carton in order to protect from light.

te taking a pre-filled pen from the refrigerator, wait approximately 15-30 minutes to allow the LIL MIOR solution in the pen to reach room temperature. Do not warm in any other way. Immediate use is then recommended.

LIFMIOR may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that LIFMIOR is removed from the refrigerator and the date after which LIFMIOR should be discarded (no more than 4 weeks following the removal from the refrigerator).

Inspect the solution in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or

almost transparent particles of protein. This appearance is normal for LIFMIOR. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

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 LIFMIOR contains

The active substance in LIFMIOR is etanercept. Each MYCLIC pre-filled pen contains 50 mg etanercept.

The other ingredients are sucrose, sodium chloride, L-arginine hydrochloride, sodium prosphate monobasic dihydrate and sodium phosphate dibasic dihydrate, and water for injections.

### What LIFMIOR looks like and contents of the pack

LIFMIOR is supplied as a solution for injection in a pre-filled pen (MYCLIC (solution for injection). The MYCLIC pen contains a clear, colourless to pale yellow or pale brown, solution for injection. Each pack contains 2, 4 or 12 pens and 2, 4 or 12 alcohol swabs. Not alwack sizes may be marketed.

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Manufacturer:

Wyeth Pharmaceuticals New Lane Havant Hampshire, PO9 2NG United Kingdom Pfizer Manufacturing Belgium NV Rijksweg 12, 2870 Puurs Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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### This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: <a href="http://www.ema.europa.eu">http://www.ema.europa.eu</a>

### 7. Using the MYCLIC pre-filled pen to inject LIFMIOR

This section is divided into the following subsections:

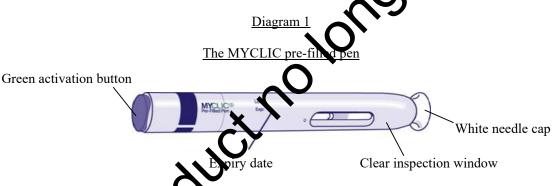
### Introduction

- Step 1: Preparing for an LIFMIOR injection
- Step 2: Choosing an injection site
- **Step 3: Injecting the LIFMIOR solution**
- Step 4: Disposing of the used MYCLIC pen

### Introduction

The instructions below explain how to use the MYCLIC pen to inject LIFMIOR. Hense read the instructions carefully, and follow them step by step. Your doctor or nurse will tell you how to inject LIFMIOR. Do not attempt to administer an injection until you are sure that you understand how to use the MYCLIC pen properly. If you have questions about how to inject please ask your doctor or nurse for help.

Morised



Step 1: Preparing for an LIEMIOR injection

- 1. Select a clean, well-lik flat surface
- 2. Gather the items that you will need for your injection, and place them on the chosen surface:
  - a. The MYCLIC pre-filled pen and one alcohol swab (take these from the carton of pens you keep in your refrigerator). Do not shake the pen.

One cotton ball or gauze

the k the expiry date (month/year) on the pen. If the date has passed, do not use the pen and contact your pharmacist for assistance.

Inspect the solution in the pen by looking through the clear inspection window. The solution should be clear or slightly opalescent, colourless to pale yellow or pale brown, and may contain small white or almost transparent particles of protein. This appearance is normal for LIFMIOR. Do not use the solution if it is discoloured, cloudy, or if particles other than those described above are present. If you are concerned with the appearance of the solution, then contact your pharmacist for assistance.

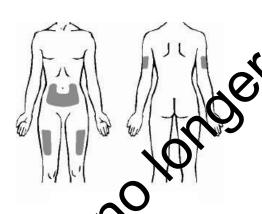
5. Leave the white needle cap in place and wait approximately 15-30 minutes to allow the LIFMIOR solution in the pen to reach room temperature. Waiting until the solution reaches room temperature may make the injection more comfortable for you. Do not warm in any other way. Always leave the pen out of sight and reach of children.

Whilst waiting for the solution in the pen to reach room temperature, read Step 2 (below), and choose an injection site.

### Step 2: Choosing an injection site (see Diagram 2)

1. The recommended injection site is the middle of the front of the thighs. If you prefer, you may alternatively use the stomach area, but make sure you choose a site at least 5 cm away from the belly button (navel). If someone else is giving you the injection, the outer area of the upper arm may also be used.





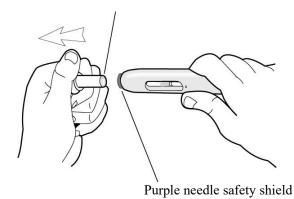
- 2. Each injection should be given at least 3 cm from where you last injected. Do not inject into tender, bruised or hard skin. Avoid scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)
- 3. If you have psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin.

### **Step 3: Injecting the LIFM Of solution**

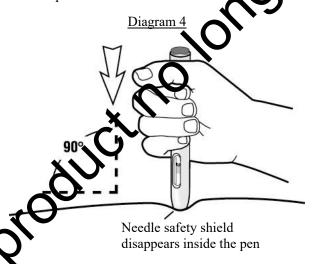
- 1. After waiting approximately 15-30 minutes for the solution in the pen to warm to room temperature, wash you'r hands with soap and water.
- 2. Clean the injection site with the alcohol swab using a circular motion, and allow it to dry. Do not touch this a criagain before injecting.
- 3. Pick up he pen, and remove the white needle cap by pulling it straight off (see Diagram 3). To avoid camaging the needle inside the pen, do not bend the white needle cap while you are removing it, and to not re-attach it once it has been removed. After removal of the needle cap, you will see a purple peedle safety shield extending slightly from the end of the pen. The needle will remain protected inside the pen until the pen is activated. Do not use the pen if it is dropped with the needle cap off.

### Diagram 3

### White needle cap

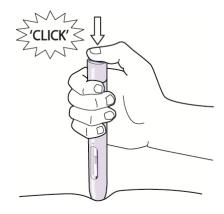


- 4. Lightly pinching the skin around the injection site between the thumb and index fix zer of your free hand may make the injection easier and more comfortable.
- 5. Hold the pen at a right angle (90°) to the injection site. Push the open ent of the pen firmly against the skin, so that the needle safety shield is pushed completely inside if his pen. A slight depression in the skin will be seen (see Diagram 4). The pen can only be activated when the needle shield is completely pushed inside the pen.

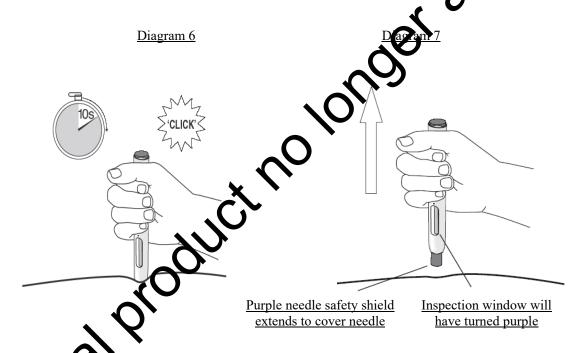


- 6. Whilst pushing he pen firmly against the skin to ensure that the needle safety shield is fully depressed it size the pen, press the centre of the green button on top of the pen with your thumb to tax the injection (see Diagram 5). On pressing the centre of the button, you will hear a click. Continue to hold the pen firmly against your skin until you hear a second click, or until 10 seconds after the first click (whichever happens first).
  - Note If you are unable to start the injection as described, press the pen more firmly against your skin, then press the green button again.

### Diagram 5

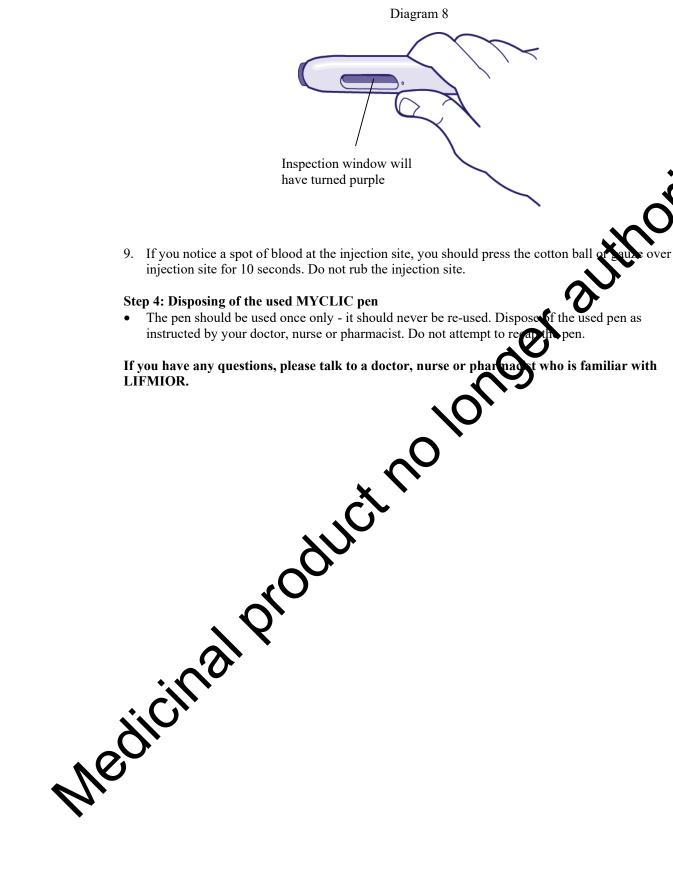


7. On hearing the second 'click' (or, if you do not hear a second 'click', after 10 seconds have passed), your injection will be complete (see Diagram 6). You may now lift the per from your skin (see Diagram 7). As you lift the pen, the purple needle safety shield will automatically extend to cover the needle.



8. The peak it election window should now be completely purple, confirming that the dose has been injected correctly (see Diagram 8). If the window is not completely purple, contact your nurse or pharm east for assistance, since the pen may not have injected the LIFMIOR solution completely.

Let not try to use the pen again, and do not try to use another pen without agreement from your nurse or pharmacist.



# Package Leaflet: Information for the User

# LIFMIOR 10 mg powder and solvent for solution for injection for paediatric use Etanercept

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

# Read all (both sides) 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 Alert Card, which contains important safety information that you need to be aware of before and during treatment with LIFMIOR.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for a child in your care. Do not pass it on to other all may harm them, even if their signs of illness are the same as those of the child you are calling or.
- If you get any side effects, talk to your doctor or pharmacist. This includes any cossible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

Information in this leaflet is organised under the following 7 section

- 1. What LIFMIOR is and what it is used for
- 2. What you need to know before you use LIFMIOR
- 3. How to use LIFMIOR
- 4. Possible side effects
- 5. How to store LIFMIOR
- 6. Contents of the pack and other information
- 7. Instructions for preparing and giving an injection of LIFMIOR (See overleaf)

#### 1. What LIFMIOR is and west till used for

LIFMIOR is a medicine that is nade from two human proteins. It blocks the activity of another protein in the body that causes in an action. LIFMIOR works by reducing the inflammation associated with certain diseases.

LIFMIOR is prescribed for the treatment of the following diseases in children and adolescents

- For the following types of juvenile idiopathic arthritis when treatment with methotrexate has not worked well enough or is not suitable for them:
  - Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in patients from the age of 2 years
  - Psoriatic arthritis in patients from the age of 12 years
- For enthesitis-related arthritis in patients from the age of 12 years when other widely used treatments have not worked well enough or are not suitable for them
- Severe psoriasis in patients from the age of 6 years who have had an inadequate response to (or are unable to take) phototherapies or other systemic therapies.

# 2. What you need to know before you use LIFMIOR

#### Do not use LIFMIOR

- if the child you are caring for is allergic to etanercept or any of the other ingredients of LIFMIOR (listed in section 6). If the child experiences allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more LIFMIOR, and contact your doctor immediately.
- if the child has, or is at risk of developing a serious blood infection called sepsis. If you are not sure, please contact your doctor.
- if the child has an infection of any kind. If you are not sure, please talk to your doctor.

# Warnings and precautions

Talk to your doctor before taking LIFMIOR.

- Allergic reactions: If the child experiences allergic reactions such as chest tightness, wheezing, dizziness or rash, do not inject more LIFMIOR, and contact your doctor in an ideally.
- Infections/surgery: If the child develops a new infection, or is about to have my major surgery, the doctor may wish to monitor the child's treatment with LIFMIOR.
- Infections/diabetes: Tell your doctor if the child has a history of courrent infections, or suffers from diabetes or other conditions that increase the risk of infection.
- Infections/monitoring: Tell your doctor of any recent travel outs to the European region. If the child develops symptoms of an infection such as fever, childs are eagh, notify your doctor immediately. Your doctor may decide to continue to notife the child for the presence of infections after the child stops using LIFMIOR.
- Tuberculosis: As cases of tuberculosis have been reported in patients treated with LIFMIOR, your doctor will check for signs and symptoms of tuberculosis before starting LIFMIOR. This may include a thorough medical history, a crest x-ray and a tuberculin test. The conduct of these tests should be recorded on the Patient Alert Card. It is very important that you tell your doctor if the child has ever had tuberculosis, or has been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (such as persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy, tell your doctor immediately.
- Hepatitis B: Tell your do tor) If the child has or has ever had hepatitis B. Your doctor should test for the presence of he autis B infection before the child begins treatment with LIFMIOR. Treatment with LIFMIOR may result in reactivation of hepatitis B in patients who have previously been an each with the hepatitis B virus. If this occurs, you should stop using LIFMIOR.
- **Hepatitis** C. Tell your doctor if the child has hepatitis C. Your doctor may wish to monitor the treatment with LIFMIOR in case the infection worsens.
- **Bloca list ders:** Seek medical advice immediately if the child has any signs or symptoms such as of sistent fever, sore throat, bruising, bleeding or paleness. Such symptoms may point to the existence of potentially life-threatening blood disorders, which may require discontinuation of MIOR
  - Nervous system and eye disorders: Tell your doctor if the child has multiple sclerosis, optic neuritis (inflammation of the nerves of the eyes) or transverse myelitis (inflammation of the spinal cord). Your doctor will determine if LIFMIOR is an appropriate treatment.
- Congestive heart failure: Tell your doctor if the child has a history of congestive heart failure, because LIFMIOR needs to be used with caution under these circumstances.
- Cancer: Tell your doctor if the child has or has ever had lymphoma (a type of blood cancer) or any other cancer before the child is given LIFMIOR.

  Patients with severe rheumatoid arthritis, who have had the disease for a long time, may be at

higher than average risk of developing lymphoma.

Children and adults taking LIFMIOR may have an increased risk of developing lymphoma or another cancer.

Some children and teenage patients who have received LIFMIOR or other medicines that work the same way as LIFMIOR have developed cancers, including unusual types, which sometimes resulted in death.

Some patients receiving LIFMIOR have developed skin cancers. Tell your doctor if the child develops any change in the appearance of the skin or growths on the skin.

- Chickenpox: Tell your doctor if the child is exposed to chickenpox when using LIFMIOR. Your doctor will determine if preventative treatment for chickenpox is appropriate.
- **Alcohol abuse**: LIFMIOR should not be used for the treatment of hepatitis related to alcohol abuse. Please tell your doctor if the child in your care has a history of alcohol abuse.
- Wegener's granulomatosis: LIFMIOR is not recommended for the treatment of Wegener's granulomatosis, a rare inflammatory disease. If the child in your care has Wegener's granulomatosis, talk to your doctor.
- Anti-diabetic medicines: Tell your doctor if the child has diabetes or is taking medicine
  treat diabetes. Your doctor may decide if the child needs less anti-diabetic medicine who
  taking LIFMIOR.

#### Children and adolescents

- Vaccinations: If possible, children should be up to date with all vaccinations before using LIFMIOR. Some vaccines, such as oral polio vaccine, should not be given while using LIFMIOR. Please consult the child's doctor before the child receive any vaccines.
- Inflammatory bowel disease (IBD): There have been cases of BA in patients with juvenile idiopathic arthritis (JIA) treated with LIFMIOR. Tell the doctor if the child develops any abdominal cramps and pain, diarrhoea, weight loss or blood in the stool.

LIFMIOR should not normally be used in children with pull arthritis or extended oligoarthritis below the age of 2 years, or in children with enthesitis-related arthritis or psoriatic arthritis below the age of 12 years, or in children with psoriasis below the age of a years.

#### Other medicines and LIFMIOR

Tell the doctor or pharmacist if the child is taking, has recently taken or might take any other medicines (including anakinra, abatacent sulfasalazine), even those not prescribed by the child's doctor. The child should not use NF AIOR with medicines that contain the active substance anakinra or abatacept.

#### Pregnancy and breast-feeding

LIFMIOR should only be used during pregnancy if clearly needed. You should consult your doctor if you become pregnant, think you may be pregnant, or are planning to have a baby.

If you received UFMIOR during pregnancy, your baby may have a higher risk of getting an infection. In addition one study found more birth defects when the mother had received LIFMIOR in pregnancy, compared with mothers who had not received LIFMIOR or other similar medicines

(TVI) and agonists), but there was no particular kind of birth defect reported. Another study found no increased risk of birth defects when the mother had received LIFMIOR in pregnancy. Your doctor will bell you to decide whether the benefits of treatment outweigh the potential risk to your baby. It is important that you tell the baby's doctors and other healthcare professionals about the use of LIFMIOR during pregnancy before the baby receives any vaccine (for more information see section 2, "Vaccinations").

Women using LIFMIOR should not breast-feed, since LIFMIOR passes into human breast milk.

# **Driving and using machines**

The use of LIFMIOR is not expected to affect the ability to drive or use machines.

#### 3. How to use LIFMIOR

#### Use in children and adolescents

Always use this medicine exactly as the doctor has told you. Check with the doctor or pharmacist if you are not sure.

If you feel that the effect of LIFMIOR is too strong or too weak, talk to your doctor or pharmacist.

The appropriate dose and frequency of dosing for the child or adolescent will depend on body weight and disease. The doctor will provide you with detailed directions for preparing and measuring the appropriate dose.

The 10 mg vial is for children prescribed a dose of 10 mg or less. Each vial should be use for just one dose in one patient, and any remaining solution should be discarded.

For polyarthritis or extended oligoarthritis in patients from the age of 2 years, or atherits-related arthritis or psoriatic arthritis in patients from the age of 12 years, the usual dose is 0.5 mg of LIFMIOR per kg bodyweight (up to a maximum of 25 mg) given twice weekly, or 0.8 mg of LIFMIOR per kg of bodyweight (up to a maximum of 50 mg) given once weekly.

For psoriasis in patients from the age of 6 years, the usual dose is 0.8 m, of LIFMIOR per kg bodyweight (up to a maximum of 50 mg), and should be given one weekly. If LIFMIOR has no effect on the child's condition after 12 weeks, your doctor may tell you to stop using this medicine.

# Method and route of administration

LIFMIOR is administered by an injection under the kir (by subcutaneous injection).

LIFMIOR can be taken with or without fold or drank

The powder must be dissolved before us. Detailed instructions on how to prepare and inject LIFMIOR are provided in section 7, "Instructions for preparing and giving an injection of LIFMIOR". Do not mix the LIPMIOR solution with any other medicine.

To help you remember, it may be helpful to write in a diary which day(s) of the week LIFMIOR should be used.

# If you use more LIFM R than you should

If you have use from LIFMIOR than you should (either by injecting too much on a single occasion or by using a too frequently), talk to a doctor or pharmacist immediately. Always have the outer carton of the mediane with you, even if it is empty.

# Syou forget to inject LIFMIOR

If you forget a dose, you should inject it as soon as you remember, unless the next scheduled dose is the next day; in which case you should skip the missed dose. Then continue to inject the medicine on the usual day(s). If you do not remember until the day that the next injection is due, do not take a double dose (two doses on the same day) to make up for a forgotten dose.

# If you stop using LIFMIOR

Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If any of the following happen to the child, do not give the child more LIFMIOR. Tell your doctor immediately, or go to the casualty department at your nearest hospital.

Trouble swallowing or breathing
Swelling of the face, throat, hands, or feet
Feeling nervous or anxious of feeling

- Severe rash, itching, or hives (elevated patches of red or pale sking ten itch)

Serious allergic reactions are rare. If the child has any of the above oms he/she may be having an allergic reaction to LIFMIOR, so you should seek immediate

## **Serious side effects**

If you notice any of the following, the child may need togent medical attention.

- may be accompanied by cough, shortness of Signs of **serious infections**, such as high **f** breath, chills, weakness, or a hot, red, ten ore area on the skin or joints
- Signs of blood disorders, such as bleeding, bruising, or paleness
- Signs of nerve disorders, such as numbress or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg
- Signs of heart failure or wars mile heart failure, such as fatigue or shortness of breath with activity, swelling in the at kle. a feeling of fullness in the neck or abdomen, night-time shortness of breath or counting, bluish colour of the nails or the lips
- may affect any part of the body including the skin and blood, and pend on the type and location of the cancer. These signs may include welling (with or without pain), persistent cough, presence of lumps or
- **commune reactions** (where antibodies are made that may harm normal tissues in ch as pain, itching, weakness, and abnormal breathing, thinking, sensation, or vision
- lupus or lupus-like syndrome, such as weight changes, persistent rash, fever, joint or pain, or fatigue
  - of **inflammation of the blood vessels** such as pain, fever, redness or warmth of the skin,

These are rare or uncommon side effects, but are serious conditions (some of which may rarely be fatal). If these signs occur, tell your doctor immediately, or take the child to the casualty department at your nearest hospital.

The known side effects of LIFMIOR include the following in groups of decreasing frequency:

**Very common** (may affect more than 1 in 10 people): Infections (including colds, sinusitis, bronchitis, urinary tract infections and skin infections): injection site reactions (including bleeding, bruising, redness, itching, pain, and swelling).

Reactions at the injection site (these do not occur as often after the first month of treatment). Some patients have developed a reaction at an injection site that was used before.

- Common (may affect up to 1 in 10 people): Allergic reactions; fever; rash; itching; antibodies directed against normal tissue (autoantibody formation).
- Uncommon (may affect up to 1 in 100 people):

  Serious infections (including pneumonia, deep skin infections, joint infections, blood infection, and infections at various sites); worsening of congestive heart failure; low red blood cell count, low white blood cell count, low neutrophil (a type of white blood cell) count; low blood platelet count; skin cancer (excluding melanoma); localised swelling of the skin (angioedema); hive (elevated patches of red or pale skin that often itch); eye inflammation; psoriasis (new or worsening); inflammation of the blood vessels affecting multiple organs; elevated liver blood tests (in patients also receiving methotrexate treatment, the frequency of elevated liver blood tests is common).
- Rare (may affect up to 1 in 1,000 people): Serious allergic reactions (including severe localised swelling of the skin a d wheezing); lymphoma (a type of blood cancer); leukaemia (cancer affecting the lood and bone marrow); melanoma (a type of skin cancer); combined low platelet, red, an white blood cell count; nervous system disorders (with severe muscle weakness and s symptoms similar to those of multiple sclerosis or inflammation of the nerves of the s or spinal cord); tuberculosis; new onset congestive heart failure; seizures lu, us or lupus-like syndrome d tiredness); skin rash, which may (symptoms may include persistent rash, fever, joint pa lead to severe blistering and peeling of the skin; I he roid reactions (itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes); inflammation of the liver caused by the body's own immune system (autonomune hepatitis; in patients also receiving methotrexate treatment, the frequency is was on); immune disorder that can affect the in ammation or scarring of the lungs (in patients lungs, skin and lymph nodes (sarcoidosis) the frequency of inflammation or scarring of the lungs is also receiving methotrexate treatment uncommon).
- Very rare (may affect up to hin 19,000 people): failure of the bone marrow to produce crucial blood cells.
- Not known (frequency cannot be estimated from the available data): Merkel cell carcinoma (a type of skin cances), excessive activation of white blood cells associated with inflammation (macrophage activation syndrome); recurrence of hepatitis B (a liver infection); worsening of a condition called dermatomyositis (muscle inflammation and weakness with an accompanying skin rash)

# Side effects in children and adolescents

The side iffects and their frequencies seen in children and adolescents are similar to those described

# Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. 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 LIFMIOR

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 carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator  $(2^{\circ}C - 8^{\circ}C)$ . Do not freeze.

Before preparing the LIFMIOR solution, LIFMIOR may be stored outside of the refrigerator at temperatures up to a maximum of 25°C for a single period of up to four weeks; after which, it should not be refrigerated again. LIFMIOR should be discarded if not used within four weeks after removal from the refrigerator. It is recommended that you record the date that LIFMIOR is removed from the refrigerator and the date after which LIFMIOR should be discarded (no more than 4 weeks following the removal from the refrigerator). This new expiry date should not exceed the expiry date recorder on the outer carton.

After preparing the LIFMIOR solution, immediate use is recommended. However, the solution may be used for up to 6 hours when stored at a temperature up to 25°C.

Do not use this medicine if you notice the solution is not clear or contains particles. The solution should be clear, colourless to pale yellow or pale brown, with no lumps or lakes or particles.

Do not throw away any medicines via wastewater or household was e. Ask your pharmacist how to throw away medicines you no longer use. These measures will kelp protect the environment.

# 6. Contents of the pack and other information

# What LIFMIOR contains

The active ingredient in LIFMIOR is etane tept. Each vial of LIFMIOR 10 mg powder and solvent for solution for injection for paediatric use contains 10 mg of etanercept. When reconstituted, the solution contains 10 mg/ml of etanercept.

The other ingredients are:

Powder: Mannitol (E421), syans, and trometamol.

Solvent: Water for injection.

#### What LIFMIOR looks like and contents of the pack

LIFMIOR 10 rap to ovder and solvent for solution for injection for paediatric use is supplied as a white powder with so vent for solution for injection (powder for injection). Each pack contains 4 vials, 4 pre-filled vringes of water for injections, 4 needles, 4 vial adaptors and 8 alcohol swabs.

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Manufacturer:

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# This leaflet was last revised in

Detailed information on this medicine is ble on the European Medicines Agency web site: http://www.ema.europa.eu

#### 7. Instructions for preparit d giving an injection of LIFMIOR

This section is divided in ollowing sub-sections:

- an injection
- LIFMIOR dose for injection
- drawing the LIFMIOR solution from the vial
- ing the needle on the syringe
- Hoosing an injection site
  - Preparing the injection site and injecting the LIFMIOR solution
- **Disposing of supplies**

# Introduction

The following instructions explain how to prepare and inject LIFMIOR. Please read the instructions carefully and follow them step by step. You will be instructed by the child's doctor or his/her assistant on the technique of giving an injection and on the amount to be given to the child. Do not attempt to administer an injection until you are sure that you understand how to prepare and give the injection.

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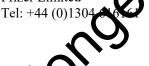
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## **Sverige**

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# **United Kingdom**

Pfizer Limited



This injection should not be mixed in the same syringe or vial with any other medicine. See section 5 for instructions on how to store LIFMIOR.

#### b. Setting up for an injection

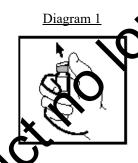
- Wash your hands thoroughly.
- Select a clean well-lit, flat working surface.
- And adaptor

  2 Alcohol swabs
  Inspect the expiry dates on both the vial label and the syringe label. They shouldn't be used after the month and year shown.

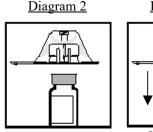
  Preparing the LIFMIOR dose for injection

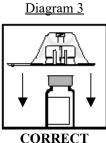
  Remove the contents of the tray
  Remove the plastic cap from the LIFMIOR topper or aluminium.

# c.



- grey stopper on the LIFMIOR vial. After cleaning, do not Use a new alcohol swab to touch the stopper with yo or allow it to touch any surface.
- Place the vial upright n, flat surface.
- Remove the paper back from the vial adaptor package.
- While still in the tic package, place the vial adaptor on top of the LIFMIOR vial so that the centered within the raised circle on top of the vial stopper (see Diagram 2).
- on the flat surface with one hand. With the other hand, push STRAIGHT LY on the adaptor package until you feel the adaptor spike penetrate the vial EEL AND HEAR THE ADAPTOR RIM LOCK INTO PLACE (see Diagram **OT** push down the adaptor at an angle (see Diagram 4). It is important that the vial spike completely penetrates the vial stopper.

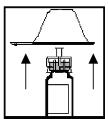






While holding the vial in one hand, remove the plastic packaging from the vial adaptor (see Diagram 5).





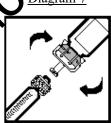
protective cover from the syringe tip by breaking the white cap along the perforation. This is done by holding the collar of the white cap while grasping the end of the white cap with the other hand and bending it down and then up until it is broken (see Di grain 6). Do NOT remove the white collar that remains on the syringe.

Diagram 6



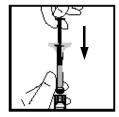
- Do not use the syringe if the perforation between the nd collar is already broken. Start again with another dose tray.
- Holding the glass barrel of the syringe (not the white collar) in one hand, and the vial adaptor (not the vial) in the other, connect the syring to the vial adaptor by inserting the tip into the opening and turn clockwise until completely secured (see Diagram 7).





- ding the vial upright on the flat surface, push the plunger VERY SLOWLY until all rent is in the vial. This will help to reduce foaming (lots of bubbles) (see Diagram 8). be the solvent is added to the LIFMIOR, the plunger may move up by itself. This is due to air pressure and should not be of concern.

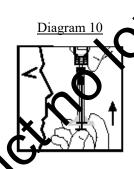
Diagram 8



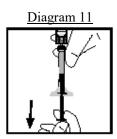
• With the syringe still attached, gently move the vial in circles a few times, to dissolve the powder (see Diagram 9). **Do NOT** shake the vial. Wait until all the powder dissolves (usually less than 10 minutes). The solution should be clear and colourless to pale yellow or pale brown, with no lumps, flakes, or particles. Some white foam may remain in the vial this is normal. **Do NOT** use LIFMIOR if all the powder in the vial is not dissolved within 10 minutes. Start again with another dose tray.



- e. Withdrawing the LIFMIOR solution from the vial
- The doctor or his/her assistant should have instructed you on the proper amount of solution to be withdrawn from the vial. If the doctor has not given this instruction, pease contact him/her.
- With the syringe still attached to the vial and vial adaptor, hold the vial upside down at eye level. Push the plunger all the way into the syringe (see Diagram 16).



• Then, slowly pull the plune of heal to draw the liquid into the syringe (see Diagram 11). Remove only the portion of liquid as directed by your child's doctor. After you have withdrawn the LIFMIOR from the val, you may have some air in the syringe. Do not be concerned, as you will remove the air in alexer step.



With the vial held upside down, unscrew the syringe from the vial adaptor by turning it anti-clockwise (see Diagram 12).

# Diagram 12



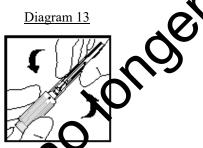
Place the filled syringe on the clean, flat surface. Make sure that the tip does not touch anything Be careful not to push down on the plunger.

Placing the needle on the syringe

The needle has been placed in a place.

# f.

- The needle has been placed in a plastic container to keep it sterile.
- To open the plastic container, hold the short, wide end in one hand. Place your & longer portion of the container.
- D'a gam 13). To break the seal, bend the larger end down and then up until broken (see



- Once the seal has been broken, remove the short, wide end of the plastic container.
- The needle will remain in the long port of the package.

  While holding the needle and contained in one hand, pick up the syringe and insert the syringe tip into the needle opening.
- turning it clockwise until completely secured (see Diagram Attach the syringe to the n 14).





Remove the needle cover by firmly pulling it straight off the syringe taking care not to touch the needle or allow the needle to touch any surfaces (see Diagram 15). Be careful not to bend or twist the cover during removal to avoid damage to the needle.

# Diagram 15



authoriser While holding the syringe upright, remove any air bubbles by slowly pushing on the plunger. until the air is removed (see Diagram 16).

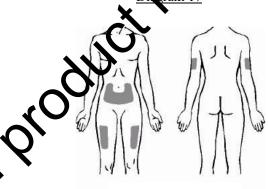
Diagram 16



#### Choosing an injection site g.

The three recommended injection sites for LIFMIOR 1) the front of the middle thighs; (2) the abdomen, except for the 5 cm area right are navel; and (3) the outer area of the upper arms (see Diagram 17). If you are self injecting you should not use the outer area of the upper arms.





ent site should be used for each new injection. Each new injection should be given at 3 cm from an old site. **Do NOT** inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks. (It may be helpful to keep notes on the location of the previous injections.)

If the child has psoriasis, you should try not to inject directly into any raised, thick, red, or scaly skin patches ("psoriasis skin lesions").

# Preparing the injection site and injecting the LIFMIOR solution

- Wipe the site where LIFMIOR is to be injected with a new alcohol swab, using a circular motion. **Do NOT** touch this area again before giving the injection.
- When the cleaned area of skin has dried, pinch and hold it firmly with one hand. With the other hand, hold the syringe like a pencil.

• With a quick, short motion, push the needle all the way into the skin at an angle between 45° and 90° (see Diagram 18). With experience, you will find the angle that is most comfortable for the child. Be careful not to push the needle into the skin too slowly, or with great force.

Diagram 18



• When the needle is completely inserted into the skin, release the skin that vo. are holding. With your free hand, hold the syringe near its base to stabilise it. Then push the puriger to inject all of the solution at a **slow**, steady rate (see Diagram 19).

Diagram 19



- When the syringe is empty, remove the needle from the skin; being careful to keep it at the same angle it was when it was inserted.
- Press a cotton ball evel-the injection site for 10 seconds. Slight bleeding may occur. **Do NOT** rub the injection site. A bandage is optional.
- i. Disposing of supplies
- The syrings and needles should **NEVER** be re-used. Dispose of the needles and syringe as irestricted by your doctor, nurse or pharmacist.
- If you have any questions, please talk to a doctor, nurse or pharmacist who is familiar with LATMIOR.