17 July 2017
EMA/114647/2016 Corr.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIFMIOR

International non-proprietary name: etanercept

Procedure No. EMEA/H/C/004167/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
AS	Ankylosing Spondylitis
ATC	Anatomical Therapeutic Chemical
eoJIA	extended oligoarticular Juvenile Idiopathic Arthritis
ERA	Enthesitis-Related Arthritis
EU	European Union
JIA	Juvenile Idiopathic Arthritis
MA	Marketing Authorization
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
nr-AxSpA	non-radiographic Axial Spondyloarthritis
NSAID	Non-Steroidal Anti-Inflammatory Drug
PsA	Psoriatic Arthritis
PSUR	Periodic Safety Update Report
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor alpha
TNFR	Tumor Necrosis Factor receptor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 21 July 2016 an application for a marketing authorisation to the European Medicines Agency (EMA) for LIFMIOR, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 January 2016.

The application concerns a generic medicinal product as defined in Article 10(1) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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 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 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 magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to 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 (PUVA) (see section 5.1).

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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data with the reference medicinal product Enbrel instead of non-clinical and clinical unless justified otherwise.

Information on paediatric requirements

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

This application is submitted as a multiple of Enbrel authorised on 03 February 2000 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form:
  - Enbrel,
  - 10 mg, 25 mg and 50 mg
  - Powder and solvent for solution for injection; Solution for injection
- Marketing authorisation holder: Pfizer Limited

- Date of authorisation: 3 February 2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/99/126/001-022

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form:
  - Enbrel,
  - 10 mg, 25 mg and 50 mg
  - Powder and solvent for solution for injection; Solution for injection
- Marketing authorisation holder: Pfizer Limited
- Date of authorisation: 3 February 2000
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/99/126/001-022

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

N/A

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: N/A

CHMP Peer reviewer: N/A

- The application was received by the EMA on 21 July 2016.
- The procedure started on 18 August 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 3 November 2016. (Annex 1). The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 2 November 2016(Annex 2).
- During the meeting on 15 December 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to LIFMIOR.

2. Scientific discussion

2.1. Introduction

Lifmior is an identical product to Enbrel, which has been authorised in the EU since 3 February 2000. The applicant, Pfizer Limited, is also the current MAH for Enbrel. Lifmior is stated to be identical to Enbrel in all but invented name and packaging.

Lifmior has all of the therapeutic indications for which Enbrel is currently approved, including treatment of:

- Moderate-to-severe active RA in adults
- Polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years
- PsA in adolescents from the age of 12 years
- Enthesitis related arthritis (ERA) in adolescents from the age of 12 years
- Active and progressive PsA in adults
- Severe active AS in adults
- Severe nr-AxSpA in adults
- Moderate-to-severe plaque psoriasis in adults
- Chronic severe plaque psoriasis in children and adolescents from the age of 6 years.

Lifmior will have the same qualitative and quantitative composition in drug substance and excipients as well as same pharmaceutical forms and dose strengths (for the 10 mg powder and solvent for solution for injection for paediatric use, 25 mg powder and solvent for solution for injection, 25 mg and 50 mg pre-filled syringe and 50 mg pre-filled pen presentations) as the reference product, Enbrel. There are no changes in the manufacturing process, manufacturers, or manufacturing sites, and container closure components for Lifmior that could lead to differences in safety or efficacy compared to Enbrel.

Etanercept belongs to the pharmacologic class of tumor necrosis factor-alpha (TNF-α) inhibitors and is a bioengineered fusion protein incorporating 2 molecules of soluble tumor necrosis factor receptor (TNFR) p75 and the crystallizable fragment (Fc) component of immunoglobulin G1 (IgG1). This human recombinant product binds specifically to TNF-α and lymphotoxin alpha, inhibiting their interaction with cell surface receptors.

The Applicant claims similarity to the originator/reference product, Enbrel (etanercept), and cross-reference is made to information submitted by the MAH for the originator product in support of this application.

No new data are therefore required for this application and none have been submitted.

2.2. Quality aspects

2.2.1. Introduction

Lifmior and Enbrel (reference product) are identical products. Lifmior is intended to have the same qualitative and quantitative composition in active substance and excipients as well as the same pharmaceutical forms and dose strengths as the reference product, Enbrel. There are no changes in the manufacturing process, manufacturers or manufacturing sites, and container closure components for Lifmior that could lead to differences in safety or efficacy compared to Enbrel. Lifmior will, in all respects, except for the invented name and packaging, be identical to the reference product Enbrel.

2.2.2. Conclusions on the chemical, pharmaceutical and biological aspects

The quality data in support of the Lifmior application are identical to the up-to-date quality data of the Enbrel dossier. All the quality data have been assessed for the Enbrel application and adequately reflected in the Product Information.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant already manufactures the same drug substance and drug product: the only difference is that this product will be branded Lifmior, whereas the approved product is branded Enbrel. Lifmior is intended to have the same qualitative and quantitative composition in drug substance and excipients as well as same pharmaceutical forms and dose strengths as the reference product, Enbrel.

The applicant has supplied a short non-clinical overview which establishes that, given this situation, no new nonclinical information is required.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

Etanercept is a human tumor necrosis factor receptor p75 FC fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. In accordance with the CHMP guidance EMEA/CHMP/SWP44447/00 entitled *"Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use"*; proteins are exempted of ERA because they are unlikely to result in a significant risk to the environment. Therefore, no environmental risk assessment was provided. This was considered acceptable by CHMP.

2.3.3. Discussion on non-clinical aspects

As the active substance in Lifmior is the same as in Enbrel, there is no requirement for the applicant to present data from non-clinical studies.

2.3.4. Conclusion on the non-clinical aspects

The application is considered acceptable regarding the non-clinical aspects.

2.4. Clinical aspects

2.4.1. Introduction

This application claims similarity to the originator/reference product, Enbrel (etanercept), and cross-reference is made to information submitted by the MAH for the originator product in support of the clinical pharmacology, efficacy and safety of Lifmior.

No new clinical data are therefore required and none have been submitted.

2.4.2. Pharmacokinetics

No new clinical pharmacology data are required for this application and none have been submitted.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

Cumulatively through 02 February 2016, it is estimated that 11,787 subjects have been exposed to etanercept (as Enbrel) either as monotherapy or in combination with comparators in Pfizer-sponsored clinical trials, and an additional 13,366 subjects have been exposed to etanercept (as Enbrel) either as monotherapy or in combination with comparators in Amgen-sponsored clinical trials.

The overall safety profile of etanercept (as Enbrel) after more than 16 years of commercial experience in the EU continues to be favourable. This is supported by the most recent etanercept PSUR with no new significant safety concerns identified during the respective time interval.

2.4.5. Discussion on clinical aspects

Etanercept is a widely used and well known active substance. Lifmior will be a duplicate authorisation for Enbrel and will therefore have exactly the same therapeutic efficacy and safety profile as Enbrel.

It has been outlined that in clinical use Lifmior may be considered interchangeable with Enbrel. This is acknowledged by CHMP considering that Lifmior is identical to Enbrel. In a broader context there is however the issue of educating health care professionals, particularly pharmacists, that Lifmior and Enbrel are

identical bearing in mind that automatic substitution for biologicals is currently not allowed in certain EU countries. The applicants' strategy to whether Lifmior is planned to be presented to be substitutable and interchangeable for Enbrel remains unclear. In this respect it should be noted that introducing an identical biological product bears the risk of adding a level of potential confusion to the existing state of education of health care professionals with regard to the issue of interchangeability and substitution of biological medicinal products, particularly biosimilars.

2.4.6. Conclusions on clinical aspects

The application is considered acceptable regarding the clinical aspects.

2.5. Risk management plan

Safety concerns

Important identified risks - all indications	Malignancy (including lymphoma and leukemia) Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection) Lupus-like reactions Sarcoidosis and/or granulomas Allergic reactions Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome) Systemic vasculitis (including ANCA positive vasculitis) Macrophage activation syndrome Central demyelinating disorders Peripheral demyelinating events (CIDP and GBS) Aplastic anemia and pancytopenia Interstitial lung disease (including pulmonary fibrosis and pneumonitis) Autoimmune hepatitis Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)
Important identified risks - specific indications/populations	Change in morphology and/or severity of psoriasis in adult and pediatric psoriasis/psoriatic arthritis populations CHF in adult subjects Inflammatory bowel disease in JIA subjects
Important potential risks - all indications	Autoimmune renal disease Pemphigus/pemphigoid Amyotrophic lateral sclerosis Myasthenia gravis Encephalitis/leukoencephalomyelitis Progressive multifocal leukoencephalopathy Liver failure Hepatic cirrhosis and fibrosis Severe hypertensive reactions Adverse pregnancy outcomes Potential for medication errors (pre-filled pen) Potential for male infertility Weight Gain

Important potential risks - specific populations	Impaired growth and development in juvenile subjects Acute ischemic CV events in adult subjects
Missing information	Not Applicable

Abbreviations: ANCA= antineutrophil cytoplasmic antibodies; CHF=congestive heart failure; CIDP=chronic inflammatory demyelinating polyneuropathy; CV=cardiovascular; GBS=Guillain-Barre Syndrome; JIA=juvenile idiopathic arthritis; TB=tuberculosis.

Pharmacovigilance plan

Study/Activity Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned/ Started)**	**Date for Submission of Final Study Report**
BSRBR Category 3	A large prospective observational study that obtains data from routine clinical practice and whose objective is to evaluate any excess risk in the occurrence of various adverse events in patients with RA, AS and PsA after allowing for confounding factors particularly of disease severity and concomitant rheumatic disease therapy.	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; Aplastic anemia and pancytopenia; CHF; Acute ischemic CV events	Started	October 2019
RABBIT Category 3	A prospective, observational cohort study whose objectives are to evaluate the long-term effectiveness, safety, and costs associated with TNF-inhibitor therapies in the treatment of RA and to compare this to a cohort of RA patients who are treated with non-biologic DMARDs.	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; Peripheral demyelinating events; Aplastic anemia and pancytopenia; CHF; PML; Acute ischemic CV events	Started	December 2017 (cohort 2)
ARTIS Category 3	A national prospective, observational, uncontrolled cohort study whose objectives are to evaluate the risk of selected adverse events in RA, JIA, and other rheumatic disease (AS and PsA) patients treated with etanercept.	Malignancy; Serious and opportunistic infections; Systemic vasculitis; Central demyelinating disorders; Aplastic anemia and pancytopenia; Interstitial lung disease; Autoimmune hepatitis; CHF; Myasthenia gravis; PML; Acute ischemic CV events	Started	May 2017

Study/Activity Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/ Started)	Date for Submission of Final Study Report
BADBIR Category 3	A long-term prospective, observational, cohort study whose objectives are to ascertain the safety and efficacy of biologic agents compared to non-biologics agents in the treatment of adult psoriasis.	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; Aplastic anemia and pancytopenia; PML	Started	July 2017
BIKER (German JIA) Category 3	A prospective observational cohort study whose aim is to describe the long-term safety, effectiveness, and cost of etanercept treatment in patients with polyarticular JIA in comparison to those treated with a conventional DMARD therapy (MTX).	Malignancy; Serious and opportunistic infections; Central demyelinating disorders; PML	Started	May 2017
20050111 (Amgen) Category 3	A multicenter, interventional, non-randomized, open-label, extension study for subjects who participated in study 20030211 to evaluate the safety of long-term administration of etanercept in pediatric subjects with moderate to severe plaque psoriasis.	Serious and opportunistic infections; Change in morphology and/or severity of psoriasis; Severe hypertensive reactions; Weight gain; Impaired growth and development in juvenile subjects; Use in different ethnic origins	Started	May 2018 or sooner (6 months after the study completion date)
B1801023 Category 3	An open-label extension study to monitor the occurrence of malignancy in pediatric subjects and to assess the long-term safety of etanercept in children and adolescents with extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis who were previously enrolled in protocol 0881A1-3338-WW (B1801014).	Malignancy; Serious and opportunistic infections; Weight gain; Impaired growth and development in juvenile subjects	Started	Approximately September 2021

Study/Activity Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/ Started)	Date for Submission of Final Study Report
PURPOSE (0881X1-4654) Category 3	A long-term, prospective, observational cohort study of the safety and effectiveness of etanercept in the treatment of paediatric psoriasis patients in a naturalistic setting.	Malignancy; Serious and opportunistic infections	Started	June 2019
B1801396	An observational cohort study to evaluate the risk of adverse pregnancy outcomes in patients treated with etanercept compared to those not treated with etanercept or other biologics using merged data from Sweden, Denmark and Finland.	Adverse pregnancy outcomes; Use in pregnant women	Planned	Final report in April 2017

Abbreviations: ARTIS=Anti-Rheumatic Therapy in Sweden; AS=ankylosing spondylitis; BADBIR=British Association of Dermatologists Biological Interventions Register; BSRBR=British Society of Rheumatology Biologics Register; CHF=congestive heart failure; CV=cardiovascular; DMARD=disease modifying anti-rheumatic drug; JIA=juvenile idiopathic arthritis; MAS=macrophage activation syndrome; MTX=methotrexate; PML=progressive multifocal; leukoencephalopathy; PSUR=periodic safety update report; RA=rheumatoid arthritis; RABBIT=German Adult Register of Biologics Users; TNF=tumor necrosis factor.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks – All indications		
Malignancy (including lymphoma and leukemia)	SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects	None proposed
Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, and parasitic infection)	SmPC section 4.3 Contraindications; SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects.	Patient alert cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to infections.
Lupus like reactions	SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects.	None proposed
Sarcoidosis and/or granulomas	SmPC section 4.8 Undesirable effects	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Allergic reactions	SmPC section 4.3 Contraindications; SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects	None proposed
Severe cutaneous adverse reactions (including toxic epidermal necrolysis and Stevens-Johnson Syndrome)	SmPC section 4.8 Undesirable effects	None proposed
Systemic vasculitis (including ANCA positive vasculitis)	SmPC section 4.8 Undesirable effects	None proposed
Macrophage activation syndrome	SmPC section 4.8 Undesirable effects	None proposed
Central demyelinating disorders	SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects	None proposed
Peripheral demyelinating events (CIDP and GBS)	SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects	None proposed
Aplastic anemia and pancytopenia	SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects	None proposed
Interstitial lung disease (including pulmonary fibrosis and pneumonitis)	SmPC section 4.8 Undesirable effects	None proposed
Autoimmune hepatitis	SmPC section 4.8 Undesirable effects	None proposed
Liver events in patients with viral hepatitis (including hepatitis B virus reactivation)	SmPC section 4.4 Special warnings and precautions	None proposed
Important Identified Risks – Specific Indications/Populations		
Change in morphology and/or severity of psoriasis in adult and pediatric psoriasis/psoriatic arthritis populations	SmPC section 4.8 Undesirable effects	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Congestive heart failure in adult subjects	SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects	Patient alert cards are provided to etanercept prescribing physicians for distribution to patients receiving etanercept. This card provides important safety information for patients, including information relating to congestive heart failure.
Inflammatory bowel disease in JIA subjects	SmPC section 4.4 Special warnings and precautions; SmPC section 4.8 Undesirable effects.	None proposed
Important Potential Risks – All Indications		
Autoimmune renal disease	None proposed	None proposed
Pemphigus/ pemphigoid	None proposed	None proposed
Amyotrophic lateral sclerosis	None proposed	None proposed
Myasthenia gravis	None proposed	None proposed
Encephalitis/ leukoencephalo-myelitis	None proposed	None proposed
Progressive multifocal leukoencephalopathy	None proposed	None proposed
Liver failure	SmPC section 4.4 Special warnings and precautions SmPC section 4.8 Undesirable effects	None proposed
Hepatic cirrhosis and fibrosis	None proposed	None proposed
Severe hypertensive reactions	None proposed	None proposed
Adverse pregnancy outcomes	SmPC section 4.6 Fertility, pregnancy and lactation	None proposed
Potential for medication errors (pre-filled pen)	Package Leaflet Instructions for use of the pre-filled pen (PFP).	Educational materials and training are given to patients, care givers and healthcare professionals (HCPs) regarding the appropriate use of the PFP.
Potential for male infertility	SmPC section 4.6 Fertility, pregnancy and lactation.	None proposed
Weight Gain	None proposed	None proposed
Important Potential Risks –Specific Populations		
Impaired growth and development in juvenile subjects	None proposed	None proposed
Acute ischemic CV events in adult subjects	SmPC section 4.8 Undesirable effect	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing Information - Not applicable.		

Conclusion

The CHMP and PRAC considered that the risk management plan version 6.2 is acceptable.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Enbrel. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(4) of Regulation No (EU) 726/2004, Lifmior (etanercept) is included in the additional monitoring list as it is a biological product to be authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

The application contains no new quality, non-clinical and clinical data. Lifmior will except for the invented name and commercial packaging, in all respects, be identical to the reference product Enbrel and will therefore have exactly the same therapeutic efficacy and safety profile as Enbrel.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of LIFMIOR is favourable in the following indication:

"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 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 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 magnetic resonance imaging (MRI) evidence, who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs).

Plaque psoriasis

Treatment of adults with moderate to 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 (PUVA) (see section 5.1).

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."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

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**

Prior to launch in each Member State, the MAH shall agree the final educational material with the competent authority in that Member State comprising of information provided to all healthcare professionals expected to prescribe the product on the correct and safe use of the pre-filled pen and a 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 pen
- A needle-free demonstration device
- Instructional materials to share with patients

The Patient's Alert Card should contain the following key elements for patients treated with LIFMIOR:

- The risk of opportunistic infections and tuberculosis (TB)
- The risk of Congestive Heart Failure (CHF).