30 May 2013
EMA/CHMP/478482/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Leflunomide medac

International non-proprietary name: leflunomide

Procedure No. EMEA/H/C/001227/X/0012/G

Note

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

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List of abbreviations

ALAT	ALanine AminoTransferase
DMARD	Disease modifying anti-rheumatic drugs
EMA	European Medicines Agency
EURD	European Union reference dates
HPLC	High performance liquid chromatography
HDPE	High density polyethylene
Ph. Eur	Pharmacopoea Europaea
PK	Pharmkokinetic
PP	Polypropylene
PSUR	Periodic Safety Update Report
RA	Rheumatoid Arthritis
RH	Relative Humidity
SPC	Summary of Product Characteristics
ULN	Upper Limit of Normal
UV	UltraViolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Medac submitted on 5 October 2012 an application for an extension of Marketing Authorisation to the European Medicines Agency (EMA) for Leflunomide medac 15 mg, film-coated tablets, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 indent c) of the Commission Regulation (EC) No 1234/2008.

Medac is already the Marketing Authorisation Holder for Leflunomide medac 10 mg and 20 mg film-coated tablets (EU/H/C/10/637/001-009). Leflunomide medac 15 mg film-coated tablets only differ in strength from the reference medicinal product (Arava - EU/1/99/118/001-10).

Leflunomide medac is used in the following indication:

- Active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD).

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure (see section 4.4) may also increase the risk of serious adverse reactions even for a long time after the switching.

The application submitted is composed of administrative information and complete quality data. In addition, the applicant submitted on 5 October 2012 the following variation(s) to the terms of the Marketing Authorisation, which are grouped with the extension of the marketing authorisation pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008:

Variation(s) requested		**Type**	**Annex(es) affected**
C.I.z	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	IAin	n/a
B.II.f.1.b.1	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	IB	I

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

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.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Leflunomide medac has been granted a Marketing Authorisation in European Union since 27 July 2010.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Martina Weise

- The application was received by the EMA on 5 October 2012.
- The procedure started on 24 October 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2013.
- The PRAC Rapporteur's RMP Assessment Report was circulated to all CHMP members on 18 January 2013.
- During the meeting on 21 February 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 February 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 March 2013.
- During the meeting on 30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of a Marketing Authorisation for Leflunomide medac.

2. Scientific discussion

2.1. Introduction

Leflunomide medac is a an immunomodulator with anti-inflammatory, analgesic, and antipyretic activity mediated primarily through inhibition of dihyroorotate dehydrogenase, an enzyme required for the de novo production of pyrimidine. Leflunomide is a prodrug which is rapidly metabolized to its active metabolite which possesses symptom-, inflammation- and structure-modifying activities in patients with active rheumatoid arthritis. It has been approved as a DMARD (disease-modifying anti-rheumatic drug) for use in patients with rheumatoid arthritis in the European Union.

Leflunomide medac was authorised as a generic medicinal product containing leflunomide as active substance. Two strengths have been already approved; 10 mg and 20 mg film-coated tablets. The additional extension application is made for Leflunomide medac 15 mg film-coated tablets. Leflunomide medac 15 mg film-coated tablets only differ in strength from the reference medicinal product. This new strength has been developed to facilitate the individual dosing of leflunomide to the patients using the already approved dosing regimen for maintenance therapy.

This application for an extension of Marketing Authorisation was grouped with a type IA_{IN} notification and a type IB variation in order to:

- extend the shelf life of 10 mg and 20 mg film-coated tablets from 30 months to 36 months (variation B.II.f.1.b.1)
- replace the Medac's DDPS with a summary of the Medac's PhV system (variation C.I.z)

Furthermore, some minor editorial changes in Section 4.4 of SmPC, in the RMP and in Module 3.2.P.2.have been introduced. Furthermore, the MAH took this occasion to update the Product Information to be in line with the QRD Template version 8.3. Both text implementations are considered acceptable by the CHMP.

In term of clinical pharmacokinetic data to support this application, based on the data from the single-dose bioequivalence study with the 20-mg formulation and using the requirements of the applicable "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", a biowaiver for the additional 15-mg strength was applied.

The active substance and the excipients used in the manufacture of the new strength are identical to those used in the manufacture of the currently approved strengths.

Concerning the chemical-pharmaceutical information reference is made, in several sections, to the information already provided for the already authorised strengths.

2.2. Quality aspects

The medicinal product is presented as film-coated tablets containing 15 mg of leflunomide as the active substance. The excipients are listed in the SmPC, section 6.1. The film-coated tablets are packed in high density polyethylene (HDPE) bottle with a screw cap including an integrated desiccant container (white silica gel).

2.2.1. Active Substance

The active substance used in the 15 mg film-coated tablets, leflunomide, is the same active substance as the one approved for the currently authorised strengths (10 mg and 20 mg).

2.2.2. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to develop an additional strength (15 mg) of immediate-release film-coated tablets. This new strength was developed to facilitate the individual dosing of leflunomide to patients. This new strength is not authorised for the reference medicinal product Arava owned by Sanofi-Aventis.

In comparison to leflunomide 10 mg and 20 mg film-coated tablets the qualitative and quantitative composition of Leflunomide medac film-coated tablets 15 mg remains unchanged and the excipients have the same functions. To guarantee a safe differentiation between the different leflunomide dosage strengths the dimension (i.e. the diameter) of the 15 mg strength has been adjusted and the leflunomide

15 mg film-coated tablets have an embossing with the number "15". Therefore, the different dosage strengths differ not only in their diameter but also in their appearance.

During the development of the additional strength a study has been initiated in order to evaluate the physical properties but also the overall *in-vitro* dissolution characteristics of leflunomide 15 mg film-coated tablets.

The 15 mg film-coated tablets are manufactured using the same process as the 10 mg and 20 mg film-coated tablets. In addition the qualitative composition of the new strength is the same and it is quantitatively proportional. In the assessed media all tested strengths (10 mg, 15 mg and 20 mg) show similar dissolution profiles. Furthermore, a comparative dissolution study on leflunomide 15 mg *versus* 20 mg film-coated tablets, in compliance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) confirmed the similarity of drug release characteristics between the new 15 mg and the 20 mg strengths.

For manufacturing and control of leflunomide film-coated tablets 15 mg the same procedures and/or analytical methods are applied as already developed, validated and approved for Leflunomide medac 10 mg and 20 mg. This approach ensures the required consistency in leflunomide film-coated tablets quality within all dosage strengths as well.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Manufacture of the product

Leflunomide medac film-coated tablets 15 mg is manufactured by using a conventional process. The manufacturing process consists of six main steps: pre-mixing, wet granulation, drying, tableting, film-coating and packaging. A detailed manufacturing description and flow scheme have been provided.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and it has been demonstrated that it is able to consistently produce a finished product of the intended quality. The in-process controls are adequate for this pharmaceutical form.
The batch analysis data on three batches show that the tablets can be manufactured reproducibly according to the agreed finished product specifications, which are suitable for control of this oral preparation.

Product specification

The finished product release and shelf-life specifications include tests for description (visual), identification (HPLC, UV), resistance to crushing (Ph. Eur.), water content (Karl Fischer method), dissolution (Ph. Eur.), assay (HPLC) and related substances (HPLC), content uniformity (Ph. Eur.) and microbiological quality (Ph. Eur.). The finished product specifications are standard for film-coated tablets.

All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the specifications. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety.
Batch analysis results on two commercial batches confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability studies have been carried out under long term (25°C/60% RH), intermediate (30°C/65% RH) and accelerated (40°C/75% RH) conditions according to the ICH requirements for two production-scale batches and two smaller-scale batches for Leflunomide medac 10 mg and 20 mg since the MAH applied for an extension of the shelf-life of the finished product from 30 months to 36 months. The batches were packaged as proposed for marketing (in white, round HDPE bottles with PP closure and mounted desiccant insert). The parameters tested and analytical methods used are identical to those used for the release specifications.

Furthermore, a photostability study was also performed on one batch of the 10 mg film-coated tablets in accordance with ICH Q1B. The film-coated tablets were exposed to light (i) without packaging, (ii) in primary packaging, and (iii) in secondary packaging applying testing conditions according to CPMP/ICH/279/95. After irradiation the Leflunomide medac 10 mg film-coated tablets directly exposed to (UV) light show no changes in their physical or chemical properties. The data demonstrates that the film-coated tablets are not sensitive to light.

Based on available stability data for 10 mg and 20 mg, the proposed shelf-life and storage conditions as stated in the SmPC were accepted.

As already mentioned the formulations of Leflunomide medac 10 mg, 15 mg and 20 mg are proportional. Furthermore, all the strengths are stored in the identical type of packaging. A bracketing approach was selected for stability testing of the additional strength (15 mg). The CHMP agreed with the bracketing approach since the stability of Leflunomide medac 15 mg is sufficiently represented by the stability data of the "extremes" (i.e. 10 mg and 20 mg film-coated tablets). The justification for the bracketing approach is in compliance with the Note for Guidance on Bracketing and Matrixing Design for Stability Testing of Drug Substances and Drug Products (CPMP/ICH/4104/00).

An in-use study has been conducted for 10 mg and 20 mg to establish a shelf-life for Leflunomide medac after the first opening of the container. Based on the study results a shelf-life of at least 100 days for the 10 mg strength and a shelf life of at least 200 days for 20 mg dosage after first opening of container was accepted by the CHMP.

Due to the bracketing design used for Leflunomide medac 15 mg, it is considered that the in-use results generated on Leflunomide medac 10 mg are representative for the 15 mg dosage strength as well. Therefore, a shelf life of at least 100 days is justified for Leflunomide medac 15 mg after first opening of the container.

Based on available stability data, the proposed shelf-life and storage conditions for the 10 and 20 mg are also acceptable for the new strength.

2.2.3. Discussion on chemical, pharmaceutical and biological aspects

Data on development, manufacture and control of this new strength of 15 mg film-coated tablets has been presented in a satisfactory manner. The new strength was developed to facilitate the individual dosing of leflunomide to the patients. This new strength is not authorised for the reference medicinal product Arava owned by Sanofi-Aventis. The qualitative and quantitative composition of the new strength is proportional to the strengths already authorised (10 mg and 20 mg). There is no novel excipient used in the formulation. All excipients are compendial, i.e. controlled to the requirements of the current Ph. Eur. monographs. Based on the stability data the extension of the shelf-life of the authorised 10 mg and 20 mg film-coated tablets from 30 months to 36 months and the minor changes in Module 3.2.P.2. are accepted by the CHMP. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the medicinal product should have a satisfactory and uniform clinical performance.

Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided, the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.4. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

Leflunomide medac was authorised as a generic medicinal product containing leflunomide as active substance.

Leflunomide is an immunomodulator with anti-inflammatory, analgesic, and antipyretic activity mediated primarily through inhibition of dihydroorotate dehydrogenase, an enzyme required for the de novo production of pyrimidine. Leflunomide is a prodrug which is rapidly metabolized to its active metabolite which possesses symptom-, inflammation- and structure-modifying activities in patients with active rheumatoid arthritis. It has been approved as a DMARD (disease-modifying anti-rheumatic drug) for use in patients with rheumatoid arthritis in the European Union.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference medicinal product Arava. The impurity profile was considered acceptable.

The extension application for Leflunomide Medac 15 mg film-coated tablets concerns a new strength of 15 mg that lies within the dose-range of the already approved leflunomide formulations (10 mg and 20 mg film-coated tablets). Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Leflunomide Medac 15 mg film-coated tablets is considered unlikely to result in any significant increase in the combined sales volumes for all leflunomide-containing products and the exposure of the environment to the active substance. Thus, the environmental risk is expected to be similar and not increased. The CHMP agrees with the above.

2.3.3. Discussion and conclusion on non-clinical aspects

No new nonclinical data were submitted for this application of a new strength of leflunomide film-coated tablets. This is considered acceptable given the existing knowledge about the substance as well as the fact that the new strength lies within the dose-range of the already approved leflunomide strengths. The proposed indication and posology remain unchanged.

2.4. Clinical aspects

2.4.1. Introduction

Leflunomide, a prodrug which is rapidly metabolized to its active metabolite A77 1726, possesses symptom-, inflammation- and structure-modifying activities in patients with active rheumatoid arthritis. It has been approved as a disease-modifying anti-rheumatic drug (DMARD), owing to its symptom-, inflammation- and structure-modifying activities for use in patients with rheumatoid arthritis in the European Union. Leflunomide-containing products are available as 10 mg, 20 mg and 100 mg film-coated tablets.

The present application concerns the addition of a new strength for Leflunomide Medac. This new strength of 15 mg (film-coated tablets) is within the approved range of the available strengths for this medicinal product. The therapeutic indication and the posology remain unchanged. The objective of this development is to facilitate the individual dosing of leflunomide in accordance with the approved SmPC which states that the recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease.

The application is based on bioequivalence considerations. Relevant for the assessment is therefore the Guideline on the Investigation of Bioequivalence in its current version (CPMP/EWP/QWP/1401/98 Rev.1). The applicant did not seek scientific advice at the CHMP.

Exemption

The initially MAA for Leflunomide Medac concerned two dosages, 10 and 20mg, respectively. To support this application a single-dose bioequivalence study was provided demonstrating bioavailability of the 20

mg film-coated tablets with the reference medicinal product (study 80427). For the 10 mg formulation a waiver for additional strengths according to the Guideline on the Investigation of Bioequivalence was accepted. The results of study 80427 are briefly described underneath (Table 1).

Table 1. Results of study 80427, M1 (A771726) true values (geometric means + SD), ratios of least-square means and acceptance ranges for 90% confidence intervals for Cmax and AUC0-168h (80% - 125%)

Parameter	Geometric means ± SD		Ratios	
	Test	Reference	Point Estimator	90% Confidence Interval
C_{max} [ng/mL]	2053.27 ±299.88	2184.14 +401.32	94.53%	87.32 - 102.33 %
T_{max} [h]	3.00 ±1.61	3.04 ±1.62	n.d.	n.d.
AUC_{0-168h} [ng·h/mL]	210935.62 ±38386.43	222653.33 ±41730.67	94.85%	86.72 - 103.74 %

To support the present application for the additional 15 mg strength, a waiver in accordance with section 4.1.6 of the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 (Rev 1)) was applied.

The following requirements are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process as referred previously in this report,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths (for immediate release products, coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d) appropriate in vitro dissolution data confirm the adequacy of waiving additional in vivo bioequivalence testing. The discriminatory power of the selected dissolution method has been already demonstrated during the development of the existing 10 mg / 20 mg dosages as reported and accepted during the initial MAA. The same dissolution conditions have been used for testing of the 15mg dosage. Three different buffers of pH 1.2, pH 4.5 and pH 6.8 were used. The f2 factor calculation confirms similarity of the dissolution profile for the new 15 mg formulation in comparison to the 20 mg formulation administered in the bioequivalence study 80427.

Linear pharmacokinetic has been reported for leflunomide. According to the Guideline on the Investigation of Bioequivalence in such case the bioequivalence study should be conducted at the highest strength, i.e. leflunomide 20 mg. The conditions for a waiver for additional strengths, listed in section

4.1.6 of the Guideline on the Investigation of Bioequivalence, are hence considered fulfilled and the bioequivalence study 80427 with leflunomide 20 mg film-coated tablet is deemed applicable for the new 15 mg dosage.

2.4.1. Pharmacokinetics

A self-standing PK characterisation (single dose fasted) was undertaken for the 20 mg dosage (Study 80427) and bioequivalence was adequately demonstrated. For the new 15-mg strength a waiver has been applied as outlined above and no further study has been provided. This is considered acceptable.

2.4.2. Pharmacodynamics

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

2.4.3. Conclusions on clinical pharmacology

The current application concerns an additional strength of leflunomide immediate release tablets (15mg). A self-standing PK characterisation (single dose fasted) was undertaken for the 20 mg dosage (Study 80427). Leflunomide tablets are an immediate-release formulation for which a single-dose bioequivalence study is adequate to document the equivalence in terms of PK. The pharmacokinetic parameters of A771726 (the active metabolite of leflunomide) were linear over the dose range of 5 to 25 mg.

Compared with the 20mg dosage, the 15mg tablets are qualitatively identical and quantitatively fully dose-proportional. Extrapolation of in-vivo data obtained for the 20 mg strength to the lower dose strength 15mg is supported by in-vitro dissolution data. In conclusion, the results of study 80427 with the 20 mg formulation can be extrapolated to the 15 mg strength as the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6 are fulfilled.

2.4.4. Post Marketing Experience

No post-marketing data are available. The dosage 15mg of Leflunomide Medac has not been authorised in any country

2.4.5. Discussion on clinical aspects

Leflunomide Medac 10 mg and 20 mg is approved for treatment of “active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD)” and the same indication is requested for the 15mg dosage. The current posology in rheumatoid arthritis is as follows: “Leflunomide therapy is usually started with a loading dose of 100 mg once daily for 3 days. Omission of the loading dose may decrease the risk of adverse events (see section 5.1). The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease”. No changes in the posology for the new 15mg dosage are proposed by the applicant.

The CHMP noted that no efficacy or safety studies have been conducted with 15mg/day and the applicant was requested by the CHMP to further justify the favourable benefit-risk relationship of the 15 mg dose strength taking into account the dose responses curves for both efficacy and safety.

Clinical trials established the efficacy of the reference medicinal product using posology as currently described in Section 4.2 of the SmPC. A phase dose-finding study (Mladenovic V et al. 1995[1]) compared 3 doses of leflunomide (5mg/day, 10mg/day and 25mg/day) to placebo. Significant superiority of 10mg/day and 25mg/day of leflunomide over placebo was demonstrated for efficacy, while adverse drug reactions occurred at higher incidence in the 25mg/day group than in the 10mg/day group. Based on these findings, the optimum leflunomide dose was estimated at between 10 and 25mg/day. Population pharmacokinetic analysis of correlation between plasma drug concentration and efficacy has led to the conclusion that the optimum dose of leflunomide is 20mg/day. Thus, in all phase III studies for the reference medicinal product a maintenance dose of 20mg leflunomide have been tested. No dose adjustment was foreseen in these studies.

In a further study (Poór et al. 2004[2]) comparing the efficacy and safety profile of 10mg and 20mg leflunomide the improvements in primary and secondary endpoints for the 20mg dosage were not considered to be clinically relevant. In contrast to that, the safety results favoured the 10mg daily maintenance dose.

Results of studies outside the setting of RCTs showed high rates of dropouts due to safety reasons (e.g. 29% of patients under 20mg Leflunomide treatment in a Dutch observational study published by van Roon et al. 2004[3]) suggesting the need for optimization of the leflunomide treatment schedule. In this respect, retrospective pharmacokinetic/ pharmacodynamic analysis of the original dose finding data suggest that leflunomide should be dosed at a daily rate above 11 mg daily to obtain near maximum probability of clinical success. The relationship between Css and clinical effect showed further that to achieve the maximum probability of clinical success in 95% of patients treated with leflunomide dose rate would have to be adjusted to achieve a median A77 1726 plasma concentration of 30 mg/l, requiring a daily dose of 16 mg leflunomide.

The SmPC allows a dose adjustment between 10 mg and 20 mg, depending on the severity of the disease. A “step up” approach, increasing leflunomide daily dose from 10 mg to 15 mg based on activity of disease, can be evaluated by periodically reassessing for evidence of disease activity measured by e.g. swollen joints and CRP. It is acknowledged that no clinical studies were performed with the 15 mg tablet and thus, it is unclear whether the “step down” approach, decreasing leflunomide daily dose from 20mg to 15mg will be sufficient in case of ALT (SGPT) elevations. Therefore, the Innovator’s recommendation to down-titrate to the 10 mg (the lowest dose available) strength (SmPC section 4.4: […] *For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be considered and monitoring must be performed weekly.* […]) should be maintained and slightly changed for the new strength as follow (***added text***, ~~*deleted text*~~): “*For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction* ~~*from 20 mg*~~ *to 10 mg may be considered and monitoring must be performed weekly.*” During the procedure the MAH has changed Section 4.4 of the SmPC accordingly.

[1] Mladenovic et al, 1995, Arthritis Rheum 38(11): 1595-603
[2] Poor et al, 2004, Rheumatology 43(6): 744-9
[3] Van Roon et al, 2004, Br J Clin Pharmacol 57(6): 790–797

Summarized, the new intermediate 15 mg strength is expected to support individual patient management by adjusting the appropriate dose regimen. Sufficient guidance is provided in the SmPC to support this treatment approach in clinical practice.

2.4.6. Conclusion on clinical aspects

A bioequivalence study was performed with the 20-mg formulation and a waiver for the additional 15-mg strength is adequately justified in line with the requirements of the applicable guidance. Moreover, the applicant has further justified the favourable benefit-risk relationship of the new 15 mg dose strength and from a clinical perspective, the new 15-mg strength is considered to facilitate the patient management by allowing for an adjustment of the recommended maintenance dose depending on the severity (activity) of the disease. The approved SmPC wording for the leflunomide Medac 15 mg reflects appropriately this guidance. The CHMP concludes that the clinical aspects of 15 mg leflunomide in the claimed indication are positive and the approval of the new strength is acceptable.

2.5. Pharmacovigilance system

The MAH has submitted a signed Summary of the MAH's Pharmacovigilance System. The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. Risk Management Plan

For this line extension for the marketing authorisation of the 15 mg dose strength of Leflunomide Medac an updated risk management plan has been submitted (version 07, dated 19.02.2013)

The safety concerns as listed in the current risk management plan for Leflunomide Medac 10 mg, 15 and 20 mg are summarized in the following table.

Summary of ongoing safety concerns:

PRAC Advice

The PRAC considered that the submitted RMP for Leflunomide Medac was acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Important identified risks	Hepatic reactions Blood cytopenia Severe skin reactions Infections Interstitial lung disease Teratogenicity Hypertension Interactions with other DMARDs (methotrexate)
Important potential risks	Male-mediated fetal toxicity Lymphoproliferative disorders Progressive multifocal leukoencephalopathy Renal failure Peripheral neuropathy
Important missing information	Use in children Concomitant use of biologic DMARDs

- Pharmacovigilance plan

Safety concern	**Planned action**
Important potential risks	
▪ Hepatic reactions	Routine pharmacovigilance, special attention in PSUR
▪ Blood cytopenia	Routine pharmacovigilance
▪ Severe skin reactions	Routine pharmacovigilance
▪ Infections	Routine pharmacovigilance
▪ Interstitial lung desease	Routine pharmacovigilance, special attention in PSUR
▪ Teratogenicity	Routine pharmacovigilance, special attention in PSUR
▪ Hypertension	Routine pharmacovigilance
▪ Interactions with other DMARs (methotrexate)	Routine pharmacovigilance, special attention in PSUR
Important potential risks	
▪ Male mediated fetal toxicity	Routine pharmacovigilance
▪ Lymphoproliferative disorders	Routine pharmacovigilance, special attention in PSUR
▪ Progressive multifocal leukoencephalopathy	Routine pharmacovigilance, special attention in PSUR

▪ Renal failure	Routine pharmacovigilance, special attention in PSUR
▪ Peripheral neuropathy	Routine pharmacovigilance
Important missing information	
▪ Use in children	Routine pharmacovigilance
▪ Concomidant use of biologic DMARDs	Routine pharmacovigilance, special attention in PSUR

- Risk minimisation measures

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Important identified risks		
Hepatic reactions	Routine pharmacovigilance Special attention in PSUR	**Labeling** Contraindication in [Section 4.3] of SPC with regard to patients with impairment of liver function or with severe hypoproteinemia. Warning in [Section 4.4] of SPC stating that rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide and stating that ALT must be checked before and during treatment, providing guidance as regards the frequency of testing during treatment and patient management in the event of increased transaminases. Information in [Section 4.8] of SPC with regard to transaminase elevation, hepatitis, jaundice and severe liver injury including hepatic failure as Undesirable effect. Additionally, information in [Section 4.1] of SPC concerning the increased risk of serious adverse reactions with recent or concurrent use of hepatotoxic DMARDs (e.g. methotrexate). **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).

		Communication and Educational Program to emphasize to prescribers the importance of monitoring liver function.
Blood cytopenia	Routine pharmacovigilance	**Labeling** Contraindication in [Section 4.3] of SPC with regard to patients having significantly impaired bone marrow function or significant anemia, leukocytopenia or thrombocytopenia due to causes other than rheumatoid arthritis. Warning in [Section 4.4] of SPC stating that a complete blood cell count, including differential white blood cell count and platelets, must be performed before and during treatment and recommending that treatment with leflunomide be discontinued in the event of severe hematologic reactions, including pancytopenia, with a washout procedure to be administered (details provided). Information in [Section 4.8] of SPC on Undesirable effects. Additionally, information in [Section 4.1] of SPC concerning the increased risk of serious adverse reactions with recent or concurrent use of hematotoxic DMARDs (e.g. methotrexate). (Restricted distribution through legal status of prescription). **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis (Section 4.2 of SPC).
Severe skin reactions	Routine pharmacovigilance	**Labeling** Contraindication in [Section 4.3] of SPC with regard to patients having a hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients. Warning in [Section 4.4] of SPC stating that very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported during

		treatment with leflunomide and recommending that treatment with leflunomide be discontinued in the event of severe skin and/or mucosal reactions and washout procedure to be administered (details provided). Information in [Section 4.8] of SPC on Undesirable effects.**Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis (Section 4.2 of SPC).
Infections	Routine pharmacovigilance	**Labeling** Contraindication in [Section 4.3] of SPC with regard to patients having severe infections. Warning in [Section 4.4] of SPC stating that medications with immunosuppressive properties, like leflunomide, can cause patients to be more susceptible to infections, including opportunistic infections, recommending that treatment with leflunomide be discontinued in the event of severe uncontrolled infections, and that a washout procedure be administered in the event that severe, uncontrolled infections occur. Information in [Section 4.8] of SPC about this risk as an Undesirable effect. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis (Section 4.2 of SPC). **Communication and Educational Program** to emphasize to prescribers the immune-suppressive properties of leflunomide, the risk of infections including opportunistic infections and the contraindication for use in immuno-compromised patients.

Interstitial lung disease	Routine pharmacovigilance Special attention in PSUR	**Labeling** Warning in [Section 4.4] of SPC stating that ILD has been reported during treatment with leflunomide, that it is a potentially fatal disorder, and that pulmonary symptoms, such as cough and dyspnea, may be a reason for discontinuing treatment. Advice on administration of a washout procedure in the event of discontinuation. Information in [Section 4.8] of the SPC about this risk as an Undesirable effect. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Teratogenicity	Routine pharmacovigilance Special attention in PSUR	**Labeling** Contraindication in [Section 4.3] of SPC with regard to pregnant women, or women of child-bearing potential who are not using reliable contraception during treatment with leflunomide. Recommendations in [Section 4.6] of the SPC with regard to the use of effective contraception during and up to 2 years after treatment, and on the need to monitor menstrual status in women of childbearing potential. Instructions on the washout procedure or waiting period to be applied for women who wish to become pregnant are also provided. Reference is made to the results of the OTIS study in [Section 4.6] of the SPC. **Communication and Educational Program** to communicate the risk of teratogenicity and to emphasize the recommendation to patients to avoid pregnancy until leflunomide levels are at an appropriate level. **Ad hoc information service** to provide patients and prescribers with information on the testing of

		plasma leflunomide levels after the waiting period. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Hypertension	Routine pharmacovigilance	**Labeling** Warning in [Section 4.4] of SPC stating that blood pressure must be checked before the start of treatment with leflunomide and periodically thereafter. Information in [Section 4.8] of the SPC about this risk as an undesirable effect. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Interaction with other DMARDs (methotrexate)	Routine pharmacovigilance Special attention in PSUR	**Labeling** Indication in [Section 4.1] of SPC contains a reminder about the risk of initiating leflunomide in the event of recent or concurrent treatment with other hepatotoxic or hematotoxic DMARDs. A washout procedure is recomm-ended when switching from leflunomide to another DMARD. Warning in [Section 4.4] of SPC stating that concomitant administration of hepatotoxic or hematotoxic DMARDs (e.g. methotrexate) is not advisable. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC). **Communication and educational activities** to ensure the safe and effective use of leflunomide in the appropriate patient population, particularly with regard to combination with other DMARDs.

Important potential risks		
Male-mediated fetal toxicity	Routine pharmacovigilance	**Labeling** Warning in [Section 4.4] of SPC stating that male patients should be aware of the possibility of male-mediated fetal toxicity and recommending that reliable contraception be used during treatment with leflunomide. Instructions on the washout procedure and waiting period to be applied for men who wish to father a child are also provided. Information in [Section 4.8] referring to decreases in sperm concentration, total sperm count and rapid progressive motility as Undesirable effects. For the patient, [Section 2 of the Package Leaflet] provides counseling for male patients who wish to father a child. **Communication and Educational Program** to communicate the risk of male-mediated fetotoxicity and to emphasize washout procedure and waiting period to be applied for men who wish to father a child. **Ad hoc information service** to provide patients and prescribers with information on the testing of plasma leflunomide levels after the waiting period. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Lymphoproliferative disorders	Routine pharmacovigilance Special attention in PSUR	**Labeling** Reference in [Section 4.8] of the SPC to the fact that the risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppressive agents. **Restricted distribution** with initiation and

		supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Progressive multifocal leukoencephalopathy	Routine pharmacovigilance Special attention in PSUR	Warning in [Section 4.4] of SPC stating that rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving leflunomide among other immunosuppressants. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Renal failure	Routine pharmacovigilance Special attention in PSUR	Section 4.3 of SPC, lists renal failure as a contra-indication for treatment with leflunomide. [Section 4.8] of SPC lists renal failure as an undesirable effect with an unknown frequency. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Peripheral neuropathy	Routine pharmacovigilance	Section 4.1 of the SmPC reminds of the risk of serious adverse reactions (such as peripheral neuropathy) to immunsuppressants including leflunomide. [Section 4.8] of SPC lists peripheral neuropathy as an undesirable effect with an unknown frequency. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Important missing information		
Use in children	Routine pharmacovigilance	**Labeling** Reference in [Section 4.2] of the SPC to the fact that leflunomide is not recommended for use in

		patients below 18 years of age. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).
Interaction with biological DMARDs	Routine pharmacovigilance Special attention in PSUR	There is no specific recommendation about the concomitant use of leflunomide with biologic DMARDs in the SPC, however both types of treatment have their prescription restricted to specialists. **Restricted distribution** with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis ([Section 4.2] of SPC).

The CHMP endorsed this advice.

2.7. User consultation

The initial application for Leflunomide medac 10 mg and 20 mg film-coated tablets and the additional extension application for the intermediate 15 mg strength concern an abridged application, which cross-refers to the reference medicinal product Arava film-coated tablets owned by Sanofi-Aventis. Reference is made to the user testing of the reference medicinal product (23/04/2008 Arava-H-C-235-IA-40) and consequently a bridging report has been provided. The CHMP concluded that proposed Package Leaflet of Leflunomide medac 15 mg film-coated tablets is compliant with article 59(3) of Council Directive 2001/83EC (Consultation with Target Patient Groups).

3. Benefit-Risk Balance

The application concerns the addition of a new strength (15 mg) within the already approved range (10 mg and 20 mg). From a clinical perspective this 15 mg strength will facilitate patient management in line with the posology in the approved SmPC where it is stated that the recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease.
Bioequivalence of the medicinal product with the reference medicinal product has previously been shown for the 20 mg dosage in study 80427. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The present application is based on a justification for the extrapolation of the bioequivalence study results to the 15 mg strength, which is accepted. A positive benefit/risk balance was concluded by the CHMP for this new strength.

Together with the Line extension application for the Leflunomide Medac 15 mg, the MAH has submitted other two variations regarding extension of shelf life and a submitted signed summary of the MAH's Pharmacovigilance System which have been assessed and considered acceptable by the CHMP.

4. Recommendation

Summary of Product Characteristics (SmPC)

The SmPC is based on the reference medicinal product SmPC (Arava) which was currently actualised (EMEA/H/C/235/II/50). Section 4.4 of the SmPC has been changed as follow (**added text**, ~~deleted text~~): "*For ALT (SGPT) elevations between 2- and 3-fold the upper limit of normal, dose reduction ~~from 20 mg~~ to 10 mg may be considered and monitoring must be performed weekly.*" The current SmPC is considered acceptable from the clinical and non-clinical point of view.

Package Leaflet (PL)

The PL is based on the reference medicinal product PL which was currently actualised (EMEA/H/C/235/II/50). The submitted PL is considered acceptable from the clinical and non-clinical point of view.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Leflunomide medac in the approved indication *treatment of adult patients with active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD)* is favourable and therefore recommends the granting of the extension 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).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Leflunomide medac are provided with a physician educational pack containing the following:

- The Summary of Product Characteristics
- Physician Leaflet
- The Physician Leaflet should contain the following key messages:
- That there is a risk of severe liver injury and so regular measurement of ALT (SGPT) levels to monitor liver function is important. The information provided in the Physician Leaflet should provide information on dose reduction, discontinuation and wash out procedures.
- The identified risk of synergistic hepato- or haematotoxicity associated with combination therapy with another Disease-Modifying Antirheumatic Drug (e.g. methotrexate).
- That there is a risk of teratogenicity and so pregnancy must be avoided until leflunomide plasma levels are at an appropriate level. Physicians and patients should be made aware that there is an ad hoc advisory service available to provide information on leflunomide plasma level laboratory testing.
- The risk of infections, including opportunistic infections, and the contraindication for use in immuno-compromised patients.
- The need to counsel patients on important risks associated with leflunomide therapy and appropriate precautions when using the medicine.