EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 May 2010
EMA/481781/2010

Human Medicines Development and Evaluation

Assessment report

Leflunomide medac

International Non-proprietary Name: Leflunomide

Procedure No: EMEA/H/C/1227

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant medac, Gesellschaft für klinische Spezialpräparate mbH submitted on 8 September 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Leflunomide medac, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC, as amended.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Community on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended. During the evaluation of this application, the applicant requested to change the proposed name for this medicinal product from Leflutab to Leflunomide medac.

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: **Arava, 10 mg, film-coated tablets**
- Marketing authorisation holder: **Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany**
- Date of authorisation: **02-09-1999**
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number: **EU/1/99/118/001**

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:

- Product name, strength, pharmaceutical form: **Arava, 20 mg, film-coated tablets**
- Marketing authorisation holder: **Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany**
- Date of authorisation: **02-09-1999**
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number: **EU/1/99/118/005-008, EU/1/99/118/005-010**
- Bioavailability study number(s): **80427**

Medicinal Product which is or has been authorised in accordance with Community provisions in force used in other studies

- Not applicable

The Rapporteur appointed by the CHMP and the evaluation team were:

Rapporteur :	Dr. Martina Weise
Pharmacovigilance Rapporteur :	Dr. Barbara van Zwieten-Boot

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 8 September 2009.
- The procedure started on 23 September 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2009.
- During the meeting on 18 to 20 January 2010, 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 January 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 March 2010.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 April 2010.
- During the meeting on 17 to 20 May 2010, 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 Leflunomide medac on 20 May 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 20 May 2010.

2. Scientific discussion

2.1 Introduction

Leflunomide medac is a generic medicinal product containing leflunomide as active substance. Two strengths have been developed; 10 mg and 20 mg film-coated tablets. The reference medicinal product Arava has been centrally authorized on 2 September 1999 and is currently available as 10 mg, 20 mg and 100 mg film-coated tablets.

Leflunomide is 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.

The recommended dose for a therapy with leflunomide in rheumatoid arthritis is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily. Patients may be started on leflunomide 10 mg or 20 mg depending on the severity (activity) of the disease.

The proposed indication for Leflunomide medac is identical to the first licensed indication of the reference medicinal product Arava. However, the second indication 'active psoriatic arthritis' of Arava is deleted from the texts of this application because of patents which are still in force according to the applicant.

The applicant has developed leflunomide tablets of 10 mg and 20 mg strength and has shown bioequivalence with the reference medicinal product Arava. All the published clinical and non-clinical experience on leflunomide can be therefore transferred to the Leflunomide medac film-coated tablets.

The excipients used in the tablet core and coating of Leflunomide medac are different from those used in the reference product Arava. All excipients are of compendial quality and are standard for this type of formulation.

2.2 Quality aspects

2.2.1. Introduction

Leflunomide medac is presented as film-coated tablets containing leflunomide as active substance. Two strengths have been developed: 10 mg and 20 mg. Other ingredients are defined in the SmPC, section 6.1. The film-coated tablets are packed in a HDPE bottle with screw cap with integrated desiccant.

2.2.2. Active Substance

The chemical name of leflunomide is 5-Methyl-N-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxamide with molecular formula $C_{12}H_9F_3N_2O_2$ and relative molecular mass 270.2. It appears as a white or almost white powder that is practically insoluble in water, freely soluble in methanol and sparingly soluble in methylene chloride. Leflunomide does not contain any chiral centres, hence it does not have optical isomers. Leflunomide shows polymorphism. At least three different polymorphic forms are described for leflunomide, i.e. Form I, II and III. One polymorphic form is consistently formed during the active substance production and used in the manufacture of the finished product. There is a monograph of leflunomide in the PhEur.

- **Manufacture**

At the time of the CHMP opinion, the active substance leflunomide is supplied by one manufacturer. The manufacturer has been issued a Certificate of Suitability (CEP) with the PhEur for the manufacture of leflunomide. The manufacturing process of leflunomide, starting materials, justification of critical steps, process control and their evaluation, critical process intermediates and acceptance criteria have been evaluated by the European Directorate for the Quality of Medicines (EDQM) before granting the Certificate of Suitability. The applicant refers to this CEP for the manufacturing details of leflunomide.

- **Specification**

For the active substance specifications reference is made to the CEP. Certificates of Analysis have been provided for three batches of leflunomide manufactured by the proposed active substance manufacturer and demonstrate the compliance of quality with the PhEur monograph and the additional specifications stated on the CEP.

The active substance is also tested by the finished product manufacturer according to the methods and specifications laid down in the PhEur monograph for leflunomide. In addition to the tests described in the PhEur monograph, the following parameters are tested by the finished product manufacturer upon receipt of the active substance: residual solvents (toluene, acetone) and particle size.
Certificates of Analysis have been provided by the finished product manufacturer and show compliance with the specifications of the PhEur monograph and the additional specifications defined by finished product manufacturer.

- **Stability**

The active substance is stored in double LDPE bags which are placed in a HDPE drum. Details on the container closure system are included in the CEP. Stability results have been provided when applying for the CEP. The CEP includes a re-test period and specifies the container for storage.
In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Medicinal Product

- **Pharmaceutical Development**

The aim of the pharmaceutical development was to develop conventional-release film-coated tablets which are essentially similar and bioequivalent to the reference product Arava from Sanofi-Aventis. The reference product Arava exists as film-coated tablets containing 10 mg, 20 mg or 100 mg leflunomide. At the time of the CHMP opinion, only the two lower strengths have been developed for Leflunomide medac.

Leflunomide is practically insoluble in water. Therefore, studies have been carried out to characterize the solubility of the active substance leflunomide in pharmaceutical relevant media at 37ºC.
Leflunomide shows polymorphism. Studies demonstrated that no change in leflunomide's polymorphic form is observable, neither during manufacturing of final dosage form, nor during storage of the final dosage form.
Special efforts have been undertaken by the applicant to prevent the formation of leflunomide impurity B (teriflunomide) in the generic Leflunomide medac film-coated tablets during manufacturing and storage. The impurity profiles of Leflumonide medac film-coated tablets 20 mg have been compared with Arava 20 mg film-coated tablets. Except for impurity B both medicinal products show comparable impurity levels; Leflunomide medac features lower content of teriflunomide (impurity B).

In solid dosage forms, particle size can affect the content uniformity, dissolution and other granular characteristics such as flowability. Therefore, the particle size of different leflunomide active substance

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

batches has been determined by laser diffraction. Comparative dissolution studies on several batches of Leflunomide medac and the reference product Arava, and a bioequivalence study have been performed to ensure that the chosen particle size specification is adequate to ensure a consistent quality of the medicinal product.
A dissolution method has been developed which demonstrates to be able to detect adequately changes in leflunomide's release from the film-coated tablets. Dissolution profiles of the Leflunomide medac film-coated tablets and of Arava were determined in different media. The dissolution data confirm that the release of leflunomide from Leflunomide medac film-coated tablets 20 mg and from Arava 20 mg film-coated tablets is similar.

Leflunomide medac is developed as film-coated tablets like the reference product Arava. However, the excipients used in the tablet core and coating are different from the reference medicinal product. Compatibility studies have been performed to confirm that there are no incompatibilities between leflunomide and the chosen excipients. The excipients are well known and standard for this type of formulation.
Certificates of Analysis have been provided for all excipients proving their pharmaceutical quality. A certificate has been submitted to confirm that magnesium stearate is of vegetable origin. For lactose monohydrate the required TSE certificate has been provided. Leflunomide medac tablets are film-coated. The coating layer has the function of taste masking and protects the tablet cores from moisture and does not modify the release of leflunomide.

The formulation of the product used in the bioequivalence study is the same as the one intended for marketing. Leflunomide medac film-coated tablets were developed in two different dosage strengths, i.e. 10 mg and 20 mg, but the bioequivalence was tested and demonstrated on the 20 mg strength only. The bioequivalence study demonstrated that the 20 mg Leflunomide medac film-coated tablet is bioequivalent to Arava 20 mg film-coated tablet (see section 3.4 clinical aspects). All respective requirements are fulfilled to extrapolate the results of the bioequivalence study performed on the 20 mg strength to the 10 mg strength. In-vitro dissolution profiles of 10 mg Leflunomide medac film-coated tablets confirm similarity of active substance release to the Leflunomide medac 20 mg film-coated tablets and to the 10 mg film-coated tablet of the reference medicinal product.

Leflunomide medac film-coated tablets 20 mg have a break-mark on one side, i.e. the tablets may be subdivided in order to take half the dose per administration only or to ease the swallowing of tablets. The functionality of the score-line has been tested according to the PhEur monograph for Tablets and it was confirmed that the breakability meets the requirements set by the European Pharmacopoeia.

- **Manufacture of the Product**

Leflunomide medac film-coated tablets 10 mg and 20 mg are manufactured by using conventional granulation followed by drying. The different steps are: pre-mixing, granulating, drying, tabletting, film-coating and packaging.
The manufacturing of Leflunomide medac film-coated tablets 10 mg/20 mg is based on a common blend approach, i.e. both dosage strengths are produced only by adjusting the tablet (core) mass during compression. Adequate in-process controls have been set up. The acceptance criteria and the test methods are adequately chosen to ensure that the drug product will comply with the specification limits. A detailed manufacturing description and flow scheme have been provided. Validation results have been presented and show that the manufacturing process is reproducible and results in a medicinal product that complies with the in-process and finished product specifications.

- **Product Specification**

The finished product release and shelf-life specifications include tests for description (visual), identification (HPLC, UV), resistance to crushing (PhEur), water content (Karl Fischer), dissolution (PhEur with HPLC), assay (HPLC) and related substances (HPLC), uniformity of dosage units (PhEur) and microbiological quality (PhEur). The finished product specifications are standard for film-coated tablets. The proposed test procedures and acceptance criteria follow the principles of the ICH Q6A guideline. All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled. All excipients used in the formulation comply with the requirements of the European Pharmacopoeia. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis results comply with the proposed

specifications and confirm consistency & 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 each strength. For the production scale batches, up to nine months long term and intermediate term stability data and up to six months accelerated stability data have been provided. For the small scale batches, up to 24 months supportive long term stability data and up to six months accelerated stability data have been provided. The small scale batches have been manufactured by a manufacturer which is not mentioned in this marketing authorisation application and the results are presented as supportive data only. The production scale batches have been manufactured at the proposed site of finished product manufacture, according to the proposed process and using the active substance obtained from the proposed active substance manufacturer. 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, an in-use study has been conducted to establish a shelf life for Leflunomide medac after first opening of the container. In addition, a photostability study was 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 demonstrate that the film-coated tablets are not sensitive to light. Hence, no specific storage recommendation (label statement) is required for the Leflunomide medac film-coated tablets. In conclusion, the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC. In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, and pharmaceutical aspects "Overall conclusions and benefit/risk assessment".

Information on development, manufacture and control of the active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the product.

2.3 Non-Clinical aspects

2.3.1. Pharmacology, Pharmacokinetics and Toxicology

As the pharmacodynamic, pharmacokinetic and toxicological properties of leflunomide are well known, no further non-clinical studies are required in support of a generic marketing authorisation and therefore no new non-clinical data was provided in this application. The applicant submitted a non-clinical overview based on a literature review of the pre-clinical pharmacology, pharmacokinetic and toxicology characteristics of leflunomide which is considered adequate. No further studies are required and the applicant has justified why no such data was provided. The non-clinical properties of leflunomide are adequately summarized in the SPC which is identical to the texts of the reference medicinal product, Arava.

The generic and reference product were compared with regard to their impurity profiles, and the impurity profile of the generic medicinal product was considered acceptable.

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2.3.2. Environmental Risk Assessment

The applicant did not present an environmental risk assessment (ERA) in the application by justifying that an increase in the environmental exposure is not expected and an environmental risk assessment was deemed not necessary. This was agreed by the CHMP.

2.4 Clinical Aspects

2.4.1. Introduction

The Leflunomide medac film-coated tablets (10 and 20 mg) have been developed as a generic equivalent to the reference product Arava, approved in the EU since 1999. To support the marketing authorisation, the applicant submitted a pivotal bioequivalence (BE) study to demonstrate bioequivalence of its 20 mg Leflunomide medac film-coated tablets with the reference product of the same strength. The applicant provided a justification for the extrapolation of the bioequivalence study results to the 10 mg strength.

Scientific advice was not sought for the development program of this product. The clinical assessment took into consideration the recommendations of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) in its current version.

GCP
The pivotal study was complying with GCP, as stated by the applicant. The applicant provided a statement to the effect that clinical trial 80427 was conducted outside the Community and was carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Exemption

The applicant has applied for marketing authorisation of Leflunomide medac film-coated tablets of 10 mg and 20 mg strength but the bioequivalence was tested on the 20 mg strength only. In accordance with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 (Rev 1)) extrapolation of the BE results to another strength is acceptable under certain conditions:

Both strengths of the generic medicinal product are manufactured by the same manufacturer and process, have the same qualitative composition and the same ratio between amounts of active substance and excipients, i.e. the quantity of the formulation in the different strengths of leflunomide is linear (proportional or homothetic formulation). Also, the pharmacokinetics of the leflunomide metabolite (M1), which is the analyte for the determination of bioequivalence in the pivotal study, are linear over the range of loading and maintenance doses to be used clinically. And finally, in vitro dissolution profiles for Leflunomide medac film-coated tablets 10 mg confirming the similarity of drug substance release in comparison to Leflunomide medac film-coated tablets 20 mg (bio batch) and 10 mg strength of the reference medicinal product have also been submitted by the applicant.

As all requirements are fulfilled for Leflunomide medac film-coated tablets 10 mg / 20 mg the extrapolation of the results of the bioequivalence study performed on the 20 mg dosage to the other dosage strength is acceptable.

2.4.3. Clinical studies

To support this marketing authorisation, the applicant has submitted one bioequivalence study (study no. 80427) with Leflunomide medac 20 mg tablets (test product) and the approved reference product of the same strength (Arava (leflunomide) 20 mg tablet, Sanofi-Aventis) (Table 1).

Table 1 *Summary of leflunomide bioequivalence study no. 80427*

Study Design and Type of	**Objective(s) of the Study**	**Test Product(s); Dosage Regimen; Route of Administration**	**Number/Type of Subjects**	**Duration of Treatment**

Control				
Randomised, open-label, 1-way parallel	BE assessment (compare the rate and extent of absorption between test and reference product)	LFL administration for 1 x 20mg: Group 1: Subject 1 – 25 Group 2: Subject 26 – 50 All subject were administered the test or reference medication (as per randomization schedule) as a single dose of 1 tablet containing 20 mg leflunomide in fasting state	n = 50 (enrolled and randomized); n = 50 (completed) / healthy subjects	Single dose

2.4.4. Pharmacokinetics

- Methods

Study design

Study 80427 was a randomised, open-label, one-way parallel, bioequivalence study of the generic leflunomide 20 mg tablet and the reference product (Arava film-coated tablet) following a single 20 mg dose in healthy subjects under fasting conditions. A parallel design has been chosen for this study because of the very long elimination half-life of the active metabolite of 8 to 14 days.

Study subjects were confined to the clinical testing facility from at least 10 hours prior to drug administration until after the 24.0 hour post-dose blood draw. No food was allowed from at least 10 hours before dosing until at least 4 hours after dosing. Not less than 4 hours post-dose, and at approximately 9 hours after dosing, subjects were served a standard meal as well as a snack approximately 13 hours after dosing. With the exception of the volume administered at the time of dosing, fluids were not permitted from 1 hour pre to 2 hours post dosing; at all other times water *ad libitum* was permitted.

Blood samples of 3 ml were collected prior to study drug administration and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 48, 72, 120 and 168 hours post-dose.

The conduct of the clinical study, bioanalytic as well as pharmacokinetic and statistical analyses were performed by a contract research organisation.

The clinical study protocol and associated documents were reviewed and approved by an Institutional Review Board and the competent regulatory authority prior to start of study procedures. There were no major protocol deviations or amendments. The enrolment and treatment periods were started and finished in spring/summer 2009.

Test and reference products

Test product:	Leflunomide medac 20 mg film-coated tablet
Manufactured by:	Haupt Pharma Münster GmbH, Germany)
Batch no.:	H0632B
Manufacturing date:	January 21, 2009
Expiry date:	01/2010

The formulation of the test product used in the bioequivalence study is the same than that intended for marketing.

Reference product:	Leflunomide (Arava) 20 mg film-coated tablet
Manufactured by:	Sanofi-Aventis, Hungary
Batch no.:	8E69E
Manufacturing date:	August 29, 2008
Expiry date:	07/2011

Population studied

A total of 50 healthy subjects of both genders with a body mass index (BMI) between 19.0 and 29.0 were enrolled, randomised and dosed. There were no withdrawals or drop-outs during the study and all subjects completed the study. For all subjects the pharmacokinetic profile was adequately characterised and all 50 subjects constituted the PK and safety population.

Inclusion and exclusion criteria were acceptable for this type of study. For a specified period prior to dosing and during the study, subjects were required to abstain from food and beverages containing xanthine, grapefruit or pomelo as well as alcohol, tobacco, natural health products and soft or hard drugs. Concomitant medication use during the study was recorded. Patients were instructed not to receive live attenuated vaccine prior or within 2 weeks after study drug administration and advised not to use hormone replacement therapy from 28 days prior to study drug administration until the end of the sample collection period.

The study was conducted in 24 healthy adult sterile male (≥18 and ≤55 years of age) and 26 post-menopausal female (≥18 and ≤70 years of age), non-smokers. The average age was 52 years. According to sample size estimation, 42 subjects had to be included for achieving an 80% power of the bioequivalence study. In order to account for possible dropouts, 50 subjects were enrolled. Pheno- or genotyping was considered dispensable since biotransformation does not depend on one specific enzyme. Subjects per groups are listed in the table below.

Table 2 Summary of demographic data

		Subjects who completed the study and were included in the PK population		
Category		**A**	**B**	**Comparison A/B**
Age (years)	Mean ± SD	53 ± 9	50 ± 11	51 ± 10
	Range	40 - 69	29 - 70	29 - 70
	Median	52	51	52
	n	25	25	50
Age Groups	<18	0	0	0
	18-40	1 (4.0 %)	5 (20.0 %)	6 (12.0%)
	41-64	22 (88.0 %)	18 (72.0 %)	40 (80.0%)
	65-75	2 (8.0 %)	2 (8.0 %)	4 (8.0%)
	>75	0	0	0
Gender	Female	13 (52.0 %)	13 (52.0 %)	26 (52.0%)
	Male	12 (48.0 %)	12 (48.0 %)	24 (48.0%)
Race	Asian	0	0	0
	Black	0	0	0
	White	25 (100%)	25 (100%)	50 (100%)
	Other	0	0	0
Ethnicity	Not Hispanic	25 (100%)	25 (100%)	50 (100%)
	Hispanic	0	0	0
Height (cm)	Mean ± SD	166.5 ± 8.3	164.2 ± 8.5	165.3 ± 8.4
	Range	151.0 - 182.0	146.0 - 177.5	146.0 - 182.0
	Median	168.0	162.0	167.5
	n	25	25	50
Weight (kg)	Mean ± SD	71.9 ± 8.7	69.3 ± 10.0	70.6 ± 9.3
	Range	52.5 - 86.5	44.1 - 87.4	44.1 - 87.4
	Median	71.8	72.3	71.9
	n	25	25	50
BMI (kg/m^2)	Mean ± SD	25.9 ± 1.7	25.6 ± 2.1	25.7 ± 1.9
	Range	22.0 - 28.4	20.7 - 28.0	20.7 - 28.4
	Median	25.8	26.4	26.1
	n	25	25	50

BMI: Body Mass Index; Other: Multi-racial, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander (refer to section 14.1.3 for details)
A=Test product
B=reference product

Analytical methods

Since the parent compound, leflunomide, is a pro-drug which is rapidly converted to the active metabolite, A771726 (or M1), the latter compound was the analyte to compare rate and extent of absorption between test and the reference drug.

Plasma concentrations were analyzed by means of a validated LC-MS/MS method. The analytical method has been appropriately validated.

Pharmacokinetic Variables

The pharmacokinetic parameters $AUC_{0\text{-}168h}$ and C_{max} of the metabolite M1 (A771726) were considered as relevant pharmacokinetic variables to assess bioequivalence of test and reference. In addition, t_{max} values were evaluated.

Statistical methods

Analyses of variance (ANOVA) was performed on the metabolite's (A771726) data of AUC until 168h and C_{max} using SAS procedure. A non-parametric test (Wilcoxon's Signed-Rank test) was used to compare t_{max}. Ratios of least-square means were calculated based on pairwise comparisons of the ln-transformed AUC and C_{max} data and inter-subject CVs were determined. The pre-specified criteria for the conclusion of bioequivalence were that the 90% geometric confidence intervals of the ratio of least-squares means from the ANOVA of the ln-transformed values of both AUC_{0-t} and C_{max} should be within the range of 80% to 125%.

Results

Two subjects were withdrawn from the study prior to receiving study medication - one due to AE (rhinitis and pharyngitis), and one subject who did not respect the xanthine restriction (250 ml of coffee) required prior to the moring check-in period. This subject was subsequently enrolled as replacement for the first subject as it was assumed that the effects of one cup of coffee taken approx. 24 hours before dosing on the metabolism of lefunomide should be minimal. The subject himself was replaced by a stand-by healthy volunteer.

The pharmacokinetic parameters obtained in the 50 subjects who were included in the analysis as well as the results of the statistical analysis for ln-transformed data are presented in Table 3.

Table 3 Pharmacokinetic parameters for M1 (A771726) – 168 hours post-dose

Parameter	Geometric means ± SD		Ratios of least-square means		
	Test (Leflunomide (A))	Reference (Arava (B))	Point Estimator	90% Confidence Interval	Inter-Subject CV
AUC_{0-168h} [ng·h/ml]	210935.62 ±38386.43	222653.33 ±41730.67	94.85%	86.72 - 103.74 %	19.06%
C_{max} [ng/ml]	2053.27 ±299.88	2184.14 +401.32	94.53%	87.32 - 102.33 %	16.84%
T_{max} [h]	3.00 ±1.61	3.04 ±1.62	n.d.	n.d.	n.d.

It is generally accepted that AUC calculated until 72 hours post-dose should be relevant to assess extent of bioavailability for compounds with very long half-lives in immediate release formulations since no formulation related absorption process is anticipated beyond this time period. The applicant has provided truncated AUC_{0-72h} during the assessment procedure which showed similar variability as the originally submitted data of AUC_{0-168h} (Table 4). The ratio analysis and the 90% confidence interval confirm bioequivalence also for the AUC_{0-72h}.

Table 4 Pharmacokinetic parameters for M1 (A771726) – 72 hours post-dose

	AUC_{0-168h}	**AUC_{0-72h}**	**C_{max}**
Ratio	94.85%	94.71%	94.53%
90% Geometric CI	86.72 to 103.74%	87.22% to 102.84%	87.32 to 102.33%
Inter-Subject CV	19.06%	17.31%	16.84%

Safety data:

Both formulations were well tolerated and no SAE were reported during the study. A total of 17 treatment-emergent adverse events (TEAE) were reported by 11 of the 50 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group was as

follows: 13 TEAEs reported by 28.0% (n=7) of the 25 subjects who received generic leflunomide and 4 TEAEs reported by 16.0% (n=4) of the 25 subjects who received the reference product (Arava). The reported adverse events were mild to moderate in intensity, and none were judged significant or serious. The most commonly reported TEAE was headache (6%), an event that is listed in the SPC of the reference product as "common". All other TEAE were reported by no more than 4% (n=2) of subjects.

- **Conclusions**

Based on the presented bioequivalence study the Leflunomide medac 20 mg film-coated tablets are considered bioequivalent with the reference product, Arava 20 mg film-coated tablets.

2.4.5. Pharmacodynamics

No new pharmacodynamic data have been provided by the applicant. These data are not required for this particular application.

2.4.6. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.5. Discussion on Clinical aspects

A single-dose, open-label bioequivalence study (80427) using a parallel design under fasting conditions has performed to demonstrate bioequivalence of the test product containing 20 mg leflunomide to the reference product Arava. The applicant has justified the choice of a parallel design with the very long elimination half-life of the active metabolite. While cholestyramin may be used to accelerate drug elimination, the parallel study design was regarded the best possible option. This approach was considered acceptable. The fasted study design was considered sufficient because leflunomide administered with a high fat/high carbohydrate meal was previously found bioequivalent to administration under fasted conditions. According to the reference medicinal product's SPC the extent of absorption is not affected by concomitant food intake. Of note, since the parent compound is a prodrug and rapidly converted to the active metabolite, A771726 (or M1), the latter compound was the analyte used in the BE study. Overall, the design of this study was considered adequate for an orally administered immediate release formulation with systemic action and the chosen analyte (M1) was acceptable.

Adequate methods have been employed for bioanalytical and statistical measurements and evaluations, respectively. Protocol violations are considered minor and do not affect the outcome of the study. The study has been performed according to current standards and adequately reported.

Overall study results are in line with published data on leflunomide although the time to maximum concentrations seems significantly shorter in the current study (about 3 hours) than generally indicated (e.g. 5-24 hours). The estimated 90%-confidence intervals are within the preset acceptance range, i.e. 80-125%, for $_{AUC0\text{-}168h}$ and C_{max}. Based on the reported data, both formulations can be considered bioequivalent and expected to behave similarly *in vivo* following a single dose of 20 mg in the fasted state.

The safety profiles of both preparations are acceptable since the reported adverse events were mild or moderate in intensity, and none were judged significant or serious. All resolved without further sequelae. All events corresponded to the known safety profile of the drug. No pathological findings were recorded in the post-study physical examinations.

The results of study 80427 with 20 mg film-coated tablet can be extrapolated to other strengths (10 mg), according to conditions laid out in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) that have been met by this application.

Based on the presented bioequivalence study the leflunomide 20 mg film-coated tablets are considered bioequivalent with the reference product, Arava.

2.6. Pharmacovigilance

2.6.1. Description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

The MAH must ensure that the system of pharmacovigilance, as described in version 7 dated 4 May 2009 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

2.6.2. Risk Management Plan

The MAH submitted a risk management plan, version 03 dated 18 May 2010, which included a risk minimisation plan.

Table Summary of the risk management plan

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 effects. 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).
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). (**Restricted distribution** through legal status of prescription).
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. Warning in [Section 4.4] of SPC stating that rare cases of Progressive Multifocal Leukoencephalo-pathy (PML) have been reported in receiving leflunomide among other immunosuppressants. Information in [Section 4.8] of SPC about this risk as an Undesirable effect. (**Restricted distribution** through legal status of prescription). **Communication and Educational Program** to emphasize to prescribers the immunosupresive 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 event. (**Restricted distribution** through legal status of prescription).

Progressive Multifocal Leukoencephalo-pathy (PML)	Routine pharmacovigilance Special attention in PSUR	**Labelling** Warning in [Section 4.4] of SPC stating that rare cases of Progressive Multifocal Leukoencephalo-pathy (PML) have been reported in receiving leflunomide among other immunosuppressants. **(Restricted distribution** through legal status of prescription).
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** through legal status of prescription).
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 recommended 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. (**Restricted distribution** through legal status of prescription).
Lympho-proliferative 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** through legal status of prescription).
Renal failure	Routine pharmacovigilance Special attention in PSUR	[Section 4.8] of SPC lists renal failure as an undesirable effect with an unknown frequency.
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** through legal status of prescription).
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.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product in line with the risk minimisation activities already approved for the reference medicinal product:

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.

The Marketing Authorisation Holder (MAH) shall ensure that any changes to the safety profile of the reference medicinal product requiring changes to the Risk Management Plan or Product Information are immediately implemented for Leflunomide medac.

In order to ensure the safe and effective use of this medicinal product, there needs to be consistency between the national implementation of the risk minimisation measures for Leflunomide medac and the physician education pack already in place in the Member States for the reference medicinal product Arava. Therefore, an Annex IV to the CHMP opinion is provided to allow consistent implementation of the risk minimisation measures by the Member States.

- **PSUR**

The PSUR submission schedule should follow the PSUR schedule for the reference product, Arava.

2.7. User consultation

A user-testing has been performed for the package leaflet of the reference product, Arava. The applicant has used the user-tested package leaflet of Arava as a basis for the Leflunomide medac package leaflet and has performed a bridging study. The differences between both package leaflets are considered minor and do not affect readability. Therefore, the CHMP considers that no further user-testing is necessary for Leflunomide medac.

2.8. Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The applicant has applied for marketing authorisation for Leflunomide medac 10 mg and 20 mg film-coated tablets based on a claimed bioequivalence with a marketed reference product Arava. No nonclinical studies have been provided for this generic application but an adequate summary of the available nonclinical information for the active substance was presented. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance leflunomide; the pivotal basis forms an appropriately designed bioequivalence study comparing a single dose of the generic leflunomide 20 mg film-coated tablets with the reference product (study no. 80427). As demonstrated, the estimated 90% confidence intervals were within the pre-specified acceptance range, i.e. 80-125%, for $AUC_{0\text{-}168h}$ and C_{max}. Based on the reported data, both formulations can be considered bioequivalent.

In accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence" (CPMP/EWP/QWP/1401/98, Rev 1) the applicant provided a justification for the extrapolation of the bioequivalence study results to the 10 mg strength. This justification is considered acceptable.

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Leflunomide medac in the indication as mentioned below was favourable and therefore recommended the granting of the marketing authorisation.

Leflunomide medac is indicated for the treatment of adult patients with:

• 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.