



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Repso

International nonproprietary name: leflunomide

Procedure No. EMEA/H/C/001222

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

Medicinal product no longer authorised

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

An agency of the European Union



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Medicinal product no longer authorised

1. Background information on the procedure

1.1. Submission of the dossier

The applicant TEVA Pharma B.V. submitted on 3 September 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Repso, through the centralised procedure falling within the scope of Article 3 (3) – 'Generic of a Centrally authorised product' of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP during its meeting on 16-19 February 2009.

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 medicinal 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(3) of Directive 2001/83/EC, as amended.

The chosen reference medicinal 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/1/99/118/010**
- Bioavailability study number(s): **2008-1776**

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 was Dr. Ondřej Slanař.

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

Licensing status:

Repso has been given a Marketing Authorisation in:
Argentina on 07 October 2005

Canada on 10 December 2004
Peru on 03 May 2007
USA on 13 September 2005
Uruguay on 24 May 2006
Puerto Rico on 05 October 2010

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 3 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 August 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 October 2010.
- During the CHMP meeting on 18 to 21 October, the CHMP agreed on a List of Outstanding Issues to be addressed in writing (and/or in an oral explanation) by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 12 November 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 November 2010.
- During the meeting on 13 to 16 December, 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 Repso on 16 December 2010.

2. Scientific discussion

2.1. Introduction

Repo 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 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.

The approved indication for Repo is identical to the current indication of the reference medicinal product Arava: Leflunomide is indicated for the treatment of adult patients with:

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- active psoriatic arthritis.

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 may also increase the risk of serious adverse reactions even for a long time after the switching.

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 recommended dose for a therapy with leflunomide for patients with psoriatic arthritis is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose for patients with psoriatic arthritis is 20 mg once daily.

The applicant has developed leflunomide film-coated tablets of 10 mg and 20 mg strength and has shown bioequivalence with the reference medicinal product Arava. All the clinical and non-clinical experience on Arava is therefore relevant for Repo film-coated tablets. According to the legislation the applicant is not required to provide the results of pre-clinical tests and clinical trials if it is demonstrated that the proposed medicinal product is a generic of a reference medicinal product which is authorised for 6/10 years in a Member State or in the Community.

During the evaluation of this marketing authorisation application, the applicant changed the proposed invented name of this medicinal product from Leflunomide Teva to the invented name Repo.

2.2. Quality aspects

2.2.1. Introduction

Repo 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 or in aluminium blisters.

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 g/mol. It appears as a white or almost white crystalline powder and is practically insoluble in water, freely soluble in methanol and sparingly soluble in methylene chloride. Leflunomide is not hygroscopic, does not contain any chiral centres, hence it does not have optical isomers. Leflunomide shows polymorphism. However, only one polymorphic form is consistently formed during the active substance manufacturing and is used in the manufacture of the medicinal product. There is a monograph of leflunomide in the Ph.Eur.

Manufacture

At the time of the CHMP opinion, the active substance leflunomide used for Repso is supplied by one active substance manufacturer. Because no Ph.Eur certificate of suitability has been issued for the active substance manufactured by the proposed supplier, detailed information about the manufacturing process, control of starting materials, reagents and solvents, control of critical steps and intermediates and process development and process validation of the active substance has been supplied in the form of an active substance master file (ASMF). All manufacturing steps are adequately described. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents. All relevant impurities, degradation products and residual solvents have been appropriately characterized.

Specification

The active substance specifications proposed by the active substance manufacturer comply with the Ph.Eur monograph for leflunomide and include additional in-house methods to test for polymorphic purity, melting range, impurities (HPLC) and residual solvents (GC). The active substance specifications proposed by the medicinal product manufacturer comply with the Ph.Eur monograph for leflunomide and include additional parameters such as tests for polymorphic purity (X-Ray powder diffraction), residual solvents (GC), particle size distribution (Malvern Laser Diffraction) and density. The limit for the residual solvent toluene is set according to the ICH guidelines. Where possible, pharmacopoeial methods are used, non-pharmacopoeial methods have been satisfactorily described and validated in accordance with the ICH guidelines.

Satisfactory Certificates of Analysis have been presented. All batches were in compliance with the predefined active substance specifications. The specifications are considered adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Stability

Stability studies have been performed at long term and accelerated conditions. Up to 60 months of long term stability data and up to 6 months of accelerated stability data have been provided, confirming the stability of leflunomide. The studies are still on-going on some batches at the time of the CHMP opinion. The specifications tested were appearance, identity, assay and impurities (HPLC). The packaging used in stability trials is identical to that proposed for market. The stability data provided support the proposed retest period at the proposed packaging and storage conditions. In accordance with EU GMP guidelines¹, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

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

2.2.3. Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to develop immediate-release film-coated tablets which are essentially similar and bioequivalent to the reference product Arava. The reference medicinal product Arava exists as film-coated tablets containing 10 mg, 20 mg or 100 mg leflunomide. In the marketing authorisation application for Repso, only the two lower strengths have been included.

The excipients in Repso are not exactly the same as those of the reference medicinal product Arava. There are small differences in the excipients used in the tablet core and film-coating. The Repso tablets are coated with a non-functional colour film-coating. The formulation difference is not considered significant with regards to the performance or the safety of the generic medicinal product compared to the reference medicinal product. The excipients used in the Repso formulation are well known and widely used in the pharmaceutical industry. All excipients comply with the European Pharmacopoeia or the Commission Directives 2008/84/EC or 95/45/EC. Certificates of Analysis demonstrated that the excipients consistently meet the predefined specifications.

In vitro dissolution studies have been performed in different dissolution media at different pH and demonstrated that the Repso 10 mg and 20 mg film-coated tablets and the Arava 20 mg film-coated tablets have equivalent release of the active substance leflunomide. The discriminatory power of the dissolution test is considered adequate. The influence of the leflunomide particle size on the dissolution of the medicinal product was investigated and it was shown that the particle size of the active substance does not influence the dissolution of the medicinal product.

Comparative impurity profile studies have been performed and showed that there is no significant difference in the impurity profile compared to the reference medicinal product.

Repso film-coated tablets were developed in two different dosage strengths, i.e. 10 mg and 20 mg. The bioequivalence however, was tested and demonstrated on the 20 mg strength only. The applicant fulfilled all respective requirements to extrapolate the results of the bioequivalence study performed on the 20 mg dosage to the 10 mg strength. Therefore the biowaiver for the 10 mg strength has been granted.

Adventitious agents

A TSE declaration was submitted to confirm that magnesium stearate is of vegetable origin. Lactose monohydrate and lactose anhydrous are derived from milk and calf rennet and are compliant with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 2). No excipients derived from human origin have been used.

Manufacture of the Product

The manufacturing process for Repso film-coated tablets 10 mg and 20 mg is standard for film-coated tablets. Adequate in-process controls are performed. The acceptance criteria and the test methods are adequately chosen to ensure that the medicinal 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. These batches have the same formulation as production scale batches and same equipment has been used. Process validation on the first three production scale batches of each strength will be performed post opinion.

Leflunomide shows polymorphism. Studies demonstrated that no change in leflunomide's polymorphic form is observed during manufacturing or storage of the medicinal product.

Product Specification

The medicinal product release and shelf-life specifications include tests for description, identification of active substance and film-coating colourants, content uniformity, dissolution, assay, impurities and degradation products, and microbiological quality. The medicinal product specifications are standard for film-coated tablets. The proposed test procedures and acceptance criteria comply with the requirements of the Ph.Eur and ICH guidelines. 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. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Batch analysis data have been provided. The batches were manufactured according to the proposed manufacturing process and packed in proposed packaging material. Batch analysis results comply with the predefined 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 both the blisters and the bottles with screw cap. Up to 24 months long term, up to 12 months intermediate term and up to 6 months accelerated stability data have been provided. The parameters tested and analytical methods used are identical to those used for the release specifications, except from the identity tests and content uniformity which were not retested at end of shelf life. The methods used for assay and related substances were proven as stability indicating. The stability batches have been manufactured at the proposed site of medicinal 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. Special storage conditions have been proposed as defined in section 6.4 of the SmPC.

Photostability studies have been performed as per ICH Q1B guideline and demonstrate that the film-coated tablets are not sensitive to light.

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 guidelines¹, 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

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 medicinal product.

2.3. Non-Clinical aspects

Pharmacology, Pharmacodynamics and Toxicology

Leflunomide is a well-established medicinal product for which there is a large amount of experience supporting its safe and effective use in patients. In this generic application, non-clinical aspects were

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

therefore only evaluated based on public literature and by cross-referring to the non-clinical information available for the reference product. Relevant non-clinical safety data for Repso have been summarized in a non-clinical overview and included in section 5.3 of the SmPC which is identical to the texts of the reference medicinal product Arava. No further studies are required and the applicant has properly justified why no such data was provided.

The impurity profile of the reference medicinal product and the test product have been compared; since no significant amounts of impurities have been found in either product it can be concluded that the products are similar.

Ecotoxicity/environmental risk assessment

The applicant has considered that an ERA is not necessary since Repso is a generic medicinal product and will replace other similar medicinal product already on the market. Therefore no increase in consumption is awaited. This was acceptable for CHMP.

2.4. Clinical Aspects

2.4.1. Introduction

To support this application for generic leflunomide, the applicant has submitted one bioequivalence study (no. 2008-1776; Table 1) to determine the relative oral bioavailability of leflunomide 20 mg film-coated tablets compared with the reference product Arava in the same strength. For the 10 mg film-coated tablet the applicant has provided a justification for a biowaiver.

Table 1 Summary of study no. 2008-1776

Study type / ID	Objective(s)	Design and Type of control	Dosage regimen; Route of Admin.	Number / type of subjects
BE / No. 2008-1776	Comparative bioavailability between leflunomide 20 mg film-coated tablets (Test) and Arava 20 mg film-coated tablets (Reference) after a single-dose administration under fasting conditions.	An open label, single dose, randomised, one-period, two treatment parallel study.	Single dose, 20 mg tablet orally under fasting conditions.	Healthy, female subjects; 80 planned; 74 dosed and completed study; 71 included in PK and statistical analysis

No scientific advice from CHMP was sought for the development program of this product. The assessment took into consideration the recommendations of the Guideline on the Investigation of Bioequivalence in its current version (CPMP/EWP/QWP/1401/98 Rev. 1).

GCP

The study was complying with GCP, as claimed by the applicant. The applicant provided a statement to the effect that study no. 2008-1776 was conducted outside the Community and was carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The applicant submitted a bioequivalence study with the highest strength (20 mg tablets) and requested a biowaiver for the lower 10 mg strength. The applicant provided justification for such a biowaiver based on the facts that:

- The drug input has been shown to be linear over the therapeutic dose range
- The pharmaceutical products are manufactured by the same manufacturer and process
- The qualitative composition of the different strengths is the same
- The ratio between amounts of the active substance and excipients is the same
- The dissolution profiles are similar under identical conditions for the additional strength and the strength of the batch used in the bioequivalence study

The biowaiver request was acceptable, since the conditions set by the applicable bioequivalence guideline including comparative dissolution testing at (at least) 3 pH levels were fulfilled and sufficiently discussed by the Applicant.

2.4.2. Clinical studies

Pharmacokinetics

- *Methods*

Study design

The relative oral availability of leflunomide 20 mg tablets (Test) and the reference product Arava 20 mg tablets (Reference) was established in a randomized, single dose, parallel group bioavailability study under fasting conditions by comparing the pharmacokinetics of the active metabolite, A771726 (Table 1). The parallel group design was chosen due to the very long half-life of the substance, in accordance with the relevant bioequivalence guideline.

Plasma levels were measured from blood samples collected over a period of 72 hours after dosing.

Each subject received either a 20 mg leflunomide test tablet (n=36) or a 20 mg reference tablet (n=38) with 240 ml water after an overnight fast, according to a computer generated randomisation list.

During each study period, blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 16, 24, 48 and 72 hours after drug administration. Plasma was harvested from these samples and assayed for A771726 using a validated LC/MS/MS method.

Subjects were confined to the clinical testing facility from at least 10 hours prior to drug administration until 24 hours post-dose. Subjects fasted overnight for at least 10 hours prior to drug administration and for at least 4 hours following drug administration, at which point a standardized meal was provided. Other standardized meals were served throughout the remainder of the confinement period.

With the exception of the water ingested during drug administration, water was not allowed from one hour prior until one hour following drug administration.

The conduct of the clinical study, analytical, pharmacokinetic and statistical analyses were performed by a contract research organization. The clinical study protocol and associated documents were reviewed and approved by an Ethics Review Board and a No Objection Letter for protocol was received by Health Authorities prior to start of study procedures. The enrolment and treatment periods were started and finished between September and December 2008.

Test and reference products

<u>Test product</u> (Treatment A)	Repo 20 mg film-coated tablets
Manufactured by:	Teva Pharmaceutical Works Private Limited Company, Hungary
Batch no.:	0080708
Manufacturing date:	07/2008

<u>Reference product</u> (Treatment B)	Arava 20 mg film-coated tablet
Manufactured by:	Sanofi-Aventis Deutschland GmbH, Germany
Batch no.:	7EU2C
Expiry date:	07/2010

Population(s) studied

Seventy-four healthy female subjects aged between 42 and 65 years (mean 56 ± 5), with a body mass index (BMI) of between 20.2 and 29.9 (mean 25.6 ± 2.8) and a weight range of 47.4 to 87.0kg (mean 65.2 ± 9.3) participated in the study. Fifty-four subjects were Caucasian, 7 were Hispanic/Latino, 7 were Asian and 6 were Black. All subjects were postmenopausal or surgically sterile.

Eighty subjects were planned to be enrolled while only 78 subjects were screened. Four subjects did not meet the inclusion criteria and therefore only 74 subjects were dosed.

All subjects were judged eligible for enrolment in this study, based on medical and medication histories, demographic data, vital signs measurements, 12-lead ECG, physical examination, and clinical laboratory tests.

Analytical methods

The analyte for the pharmacokinetic evaluation in this study was the metabolite A771726. This was justified by the applicant as leflunomide is rapidly converted into this metabolite and there is no documented analytical method available which would provide reliable measurement of leflunomide

Subject plasma concentrations of the leflunomide metabolite A771726 were measured by a liquid chromatographic tandem mass spectrometric detection method. Leflunomide metabolite was shown to be stable in human plasma following three (3) freeze thaw cycles, short term and long term stability of analytes has been presented and the validation of analytical LC MSMS method is adequate.

Pharmacokinetic Variables

The pharmacokinetic parameters of interest in this study were AUC_{0-72} , C_{max} and T_{max} in respect of A771726.

Statistical methods

SAS software release 9.1 was used to analyze the data. ANOVA was carried out on ln-transformed AUC_{0-t} , C_{max} . Factors of subjects, treatments, and group were also evaluated in the model. A non-parametric test was carried out to compare the T_{max} values between treatments. Individual data were presented, logarithmic transformation used, and individual plasma concentration-time profiles were shown in the dossier. Descriptive statistics was used to summarize the results.

AUC_{0-t} and C_{max} were considered as primary parameters for bioequivalence conclusion with standard acceptance range of 80-125%.

• Results

Only 74 subjects were dosed but complete PK profiles for BE assessment were only available for 71 subjects. This was because three subjects had been excluded from the PK and BE analysis as the last time point of the AUC could not be reliably estimated due to broken 72 hour samples during centrifugation.

In addition, there were several minor protocol deviations during the conduct of the study, including delayed sample drawings and minor modification of standard meal, all of which were only considered minor.

Of the 71 female subjects included in the data analysis, 51 were Caucasian, 7 were Hispanic/Latino, 7 were Asian and 6 were Black. The mean age was 56 ± 5 yrs (42 – 65 yrs), height 159.3 ± 7.2 cm (145.0 – 182.0 cm), weight: 65.1 ± 9.3 kg (47.4 – 87.0 kg) and BMI 25.6 ± 2.8 (20.2 – 29.9).

The standard 90% CI for ln-transformed AUC_{0-72} and C_{max} values fit within standard acceptance range of 80-125% for the active metabolite A771726.

Analyte: A771726 (Treatment A: N = 34; Treatment B: N = 37)

Parameter	TRT	Means		Contrast	Ratio	90% CI		Inter-Sub CV(%)	
		Arithmetic	CV(%)			Geometric	Lower		Upper
<i>Based on Measured Data</i>									
AUC_{0-72} (ng·h/mL)	A	98719.4	(16)	97419.8	A vs. B	105.28	98.99	- 111.97	16
	B	93374.8	(15)	92533.8					
C_{max} (ng/mL)	A	1953.2	(19)	1914.6	A vs. B	101.01	93.88	- 108.68	19
	B	1926.2	(18)	1895.5					
T_{max} (h)	A	2.27	(113)						
	B	2.04	(42)						

Treatment A = Test product; Treatment B = Reference product (Arava)

Clinical safety

In study no. 2008-1776 there were 78 adverse events (AE) observed in the study, involving 33 subjects. There were several mild AE reported in the study following administration of both study drugs. No serious AEs were reported during the conduct of this study and no withdrawals due to AE occurred.

- Conclusion

Based on the presented bioequivalence study Repso 20 mg film-coated tablets is considered bioequivalent with the reference medicinal product Arava 20 mg film-coated tablets.

Pharmacodynamics

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

2.4.3. Post marketing experience

Medicinal products from Teva containing leflunomide are registered in 6 countries: Canada, Argentina, USA, Uruguay, Puerto Rico and Peru. The first registration was in Canada on 10th December 2004. Since that until 31st January 2010 the estimated patient exposure was 107,611 patient-years (39,277,899 daily doses) from all 6 countries.

Since the launch of Teva's leflunomide in North and South America, Teva received no reports of off label use. There were totally 4 reports of pregnancy (3 ended in abortion and 1 in mild intrauterine growth retardation with no other abnormalities). According to the MAH, the spectrum of reported adverse reactions is in line with the product labelling, no unexpected safety signal has been detected.

2.4.4. Discussion and conclusion of clinical aspects

The bioequivalence study no. 2008-1776 used a parallel design due to the long half-life of the substance and was conducted with conventional procedures. The conversion of leflunomide to its metabolite, A771726, is rapid and therefore very low plasma levels of parent compound have been occasionally detected. Still, there is no reliable analytical method for determination of parent compound in human plasma. Therefore leflunomide may be considered to belong to a minority of drugs for which metabolite data are adequate for the assessment of bioequivalence.

The sampling period of 72 hours was suitable to adequately characterize the concentration-time profile for bioequivalence purposes, although due to the long half-life of the analyte a complete pharmacokinetic profile could not be obtained. This sampling period is in accordance with the current bioequivalence guideline, which indicates that AUC truncated at 72h (AUC(0-72h)) may be used as an alternative to AUC(0-t) for comparison of extent of exposure as the absorption phase has been covered by 72h for immediate release formulations. The test conditions were sufficiently standardized in order to minimize the variability of all factors involved except that of the products being tested. The dose was selected according to the usual dosing recommendations and corresponds to the highest strength applied for. There were only minor deviation from protocol, there is some uncertainty connected to the description of samples lost during centrifugation, which were considered acceptable.

The patient population was chosen according to the relevant guidelines. The study has been conducted in a population of female subjects, which is considered acceptable, since there is no concern that this study population would be less sensitive for the detection of formulation-specific differences.

The analytical method, its validation and the description of the way how the samples were handled were acceptable. The sensitivity, precision, accuracy and linearity of determination are adequate and the analytical method was appropriate.

The statistics were described adequately and statistical methods used were acceptable. The primary bioequivalence conclusion is based on the standard acceptance range of 80.00-125.00% for the active metabolite A771726. The data shows that the 90% CI for In-transformed AUC_{0-72} , and C_{max} values fit within the pre-specified acceptance range.

The biowaiver for the 10 mg strength can be granted as all conditions including comparative dissolution testing at (at least) 3 pH levels have been submitted.

In summary, bioequivalence of the Repso 20 mg film-coated tablets with the reference medicinal product, Arava 20 mg film-coated tablets, has been satisfactorily demonstrated.

2.5. Pharmacovigilance

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

The applicant has submitted the Detailed Description of the Pharmacovigilance System (version 7.0, dated May 2009), which fulfils the requirements and provides adequate evidence that TEVA Europe has the services of a Qualified Person responsible for Pharmacovigilance and also has the necessary means for notification of any adverse reaction suspected of occurring either in the Community or a third country.

PSUR

The PSUR submission schedule should follow the PSUR schedule for the reference medicinal product

Description of the Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, 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.

Risk Management Plan

The MAH submitted a risk management plan, version 2 dated 2 November 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, including presentation of collated data in the	Labelling: Contraindication in [Section 4.3] of SmPC with regard to patients with impairment of liver function or with severe hypoproteinemia. Warning in [Section 4.4] of SmPC stating that rare cases of severe liver injury, including cases with fatal outcome, have been reported

	corresponding chapter of the PSUR	<p>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.</p> <p>Information in [Section 4.8] of SmPC with regard to transaminase elevation, hepatitis, jaundice and severe liver injury including hepatic failure as Undesirable effects.</p> <p>Additionally, information in [Section 4.1] of SmPC concerning the increased risk of serious adverse reactions with recent or concurrent use of hepatotoxic DMARDs (e.g. methotrexate).</p> <p>Restricted distribution with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis and psoriatic arthritis ([Section 4.2] of SmPC).</p> <p>Communication and Educational Program to emphasize to prescribers the importance of monitoring liver function.</p>
Blood cytopenia	Routine Pharmacovigilance	<p>Labelling: Contraindication in [Section 4.3] of SmPC with regard to patients having significantly impaired bone marrow function or significant anaemia, leucocytopenia or thrombocytopenia due to causes other than rheumatoid arthritis or psoriatic arthritis.</p> <p>Warning in [Section 4.4] of SmPC 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 haematologic reactions, including pancytopenia, with a washout procedure to be administered (with details provided).</p> <p>Information in [Section 4.8] of SmPC on Undesirable effects.</p> <p>Additionally, information in [Section 4.1] of SmPC concerning the increased risk of serious adverse reactions with recent or concurrent use of hematotoxic DMARDs (e.g. methotrexate).</p> <p>(Restricted distribution through legal status of prescription).</p>
Severe skin reactions	Routine pharmacovigilance	<p>Labelling: Contraindication in [Section 4.3] of SmPC with regard to patients having a hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiform) or to any of the excipients.</p> <p>Warning in [Section 4.4] of SmPC 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 (with details provided).</p> <p>(Restricted distribution through legal status of prescription).</p>
Infections (including opportunistic infections)	Routine pharmacovigilance	<p>Labelling: Contraindication in [Section 4.3] of SmPC with regard to patients having severe infections.</p> <p>Warning in [Section 4.4] of SmPC 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.</p> <p>Information in [Section 4.8] of SmPC about this risk as an Undesirable effect.</p> <p>Restricted distribution with initiation and supervision of treatment by a specialist experienced in the treatment of rheumatoid arthritis and psoriatic arthritis ([Section 4.2] of SmPC).</p> <p>Communication and Educational Program to emphasize to prescribers the immunosuppressive properties of leflunomide, the</p>

		risk of infections including opportunistic infections and the contraindication for use in immuno-compromised patients.
Interstitial lung disease	Routine pharmacovigilance, including presentation of collated data in the corresponding chapter of the PSUR	Labelling: Warning in [Section 4.4] of SmPC stating that ILD has been reported during treatment with leflunomide, which is a potentially fatal disorder, and that pulmonary symptoms, such as cough and dyspnoea, 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 SmPC about this risk as an Undesirable event. (Restricted distribution through legal status of prescription).
Teratogenicity	Routine pharmacovigilance, including presentation of collated data in the corresponding chapter of the PSUR	Labelling: Contraindication in [Section 4.3] of SmPC 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 SmPC 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. Communication and Educational Program (incl. Patient Information Sheet) 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 and psoriatic arthritis ([Section 4.2] of SmPC).
Hypertension	Routine pharmacovigilance	Labelling: Warning in [Section 4.4] of SmPC stating that blood pressure must be checked before the start of treatment with leflunomide and periodically thereafter. Information in [Section 4.8] of the SmPC about this risk as an Undesirable effect. (Restricted distribution through legal status of prescription).
Interactions with other DMARDs (methotrexate)	Routine pharmacovigilance, including presentation of collated data in the corresponding chapter of the PSUR	Labelling: Indication in [Section 4.1] of SmPC 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 SmPC 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 and psoriatic arthritis ([Section 4.2] of SmPC). Communication and Educational Program 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	Routine pharmacovigilance	Labelling: Warning in [Section 4.4] of SmPC stating that male patients should be aware of the possibility of male-mediated foetal toxicity and recommending that reliable contraception be used

toxicity		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 counselling for male patients who wish to father a child.
Lympho-proliferative disorders	Routine pharmacovigilance, including presentation of collated data in the corresponding chapter of the PSUR	Labelling: Reference in [Section 4.8] of the SmPC 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).
Progressive multifocal leukoencephalopathy	Routine pharmacovigilance, including presentation of collated data in the corresponding chapter of the PSUR	Signal still under evaluation for its relevance. No information in the SmPC. (Restricted distribution through legal status of prescription).
Renal failure	Routine pharmacovigilance, including presentation of collated data in the corresponding chapter of the PSUR	[Section 4.8] of SmPC lists renal failure as an undesirable effect with an unknown frequency.
IMPORTANT MISSING INFORMATION		
Use in children	Routine pharmacovigilance	Labelling: Reference in [Section 4.2] of the SmPC 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 and psoriatic arthritis ([Section 4.2] of SmPC).
Concomitant use of biologic DMARDs	Routine pharmacovigilance, including presentation of collated data in the corresponding chapter of the 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 specialist experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

2.6. User consultation

A user-testing has been performed for the package leaflet of the reference medicinal product, Arava. The applicant has used the user-tested package leaflet of Arava as a basis for the proposed package leaflet and has performed user testing of the Repso package leaflet. The differences between both package leaflets are considered minor and do not affect readability. The proposed package leaflet was judged acceptable.

2.7. Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The applicant has applied for marketing authorisation for Repso 10 mg and 20 mg film-coated tablets based on a claimed bioequivalence with a marketed reference medicinal 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. The efficacy, safety and clinical pharmacology of the active ingredient leflunomide are already well-established and documented for the reference medicinal product, Arava. The submitted bioequivalence study no. 2008-1776 is designed and reported in accordance with the relevant EU note for guidance on BE investigation. The primary bioequivalence conclusion is based on the 90% CI for ln-transformed AUC_{0-72} and C_{max} of the active metabolite A771726 which fit within the standard acceptance range of 80.00-125.00% and the bioequivalence to the reference product has been shown.

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 Repso in the indication as mentioned below was favourable and therefore recommended the granting of the marketing authorisation.

Repso is indicated for the treatment of adult patients with:

- * active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- * active psoriatic arthritis.

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.