European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMA/761626/2009

ASSESSMENT REPORT
FOR
LEFLUNOMIDE WINTHROP

International Nonproprietary Name:
LEFLUNOMIDE

Procedure No. EMEA/H/C/1129

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Sanofi-Aventis Deutschland GmbH submitted on 4 February 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Leflunomide Winthrop, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 25 September 2008.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder for an authorised medicinal product

The applicant applied for the following indication: "Leflunomide Winthrop is indicated in adults for the treatment of active rheumatoid arthritis (RA) as a disease modifying antirheumatic drug (DMARD) and for the treatment of active psoriatic arthritis (PsA)."

Information on Paediatric requirements:
Not applicable

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The initial product Arava, has been given a Marketing Authorisation in:
European Union, Iceland, Norway, Albania, Algeria, Argentina, Aruba, Australia, Bahrain, Belarus, Bolivia, Bosnia-Herzegovina, Botswana, Brazil, Brunei Darussalam, Canada, Chile, Colombia, Costa Rica, Croatia, Cuba, Dominican Republic, Ecuador, Egypt, El Salvador, Gabon, Ghana, Guatemala, Haiti, Honduras, Hong Kong, India, Indonesia, Israel, Jamaica, Japan, Jordan, Kazakhstan, Kenya, Republic of Korea, Kuwait, Lebanon, Macedonia, Malaysia, Mauritius, Mexico, Republic of Moldova, Morocco, Nepal, Netherlands Antilles, New Zealand, Nicaragua, Oman, Pakistan, Palestinian Territories, Panama, Paraguay, Peru, Philippines, Qatar, Russian Federation, Senegal, Serbia and Montenegro, Singapore, South Africa, Sri Lanka, Switzerland, Syrian Arab Republic, Taiwan, Thailand, Trinidad & Tobago, Tunisia, Ukraine, United States, Uruguay, Venezuela, Zimbabwe.
Pending: Bangladesh, Botswana, Namibia, Saudi Arabia
Withdrawn (by applicant after authorisation): Aruba, China, Costa Rica, Dominican Republic, Guatemala, Haiti, Ivory Coast, Jamaica, Netherlands Antilles, Thailand, Trinidad & Tobago, Uruguay, Vietnam

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

Rapporteur: Barbara van Zwieten-Boot Co-Rapporteur: Pieter Neels

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 4 February 2009.
- The procedure started on 22 February 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 1 April 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 6 April 2009.
- During the meeting on 20-23 April 2009, 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 24 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 September 2009.
- During the CHMP meeting on 21-24 September 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues on 12 October 2009.
- During the meeting on 19-22 October 2009, 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 Winthrop on 22 October 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 October 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

This application has been submitted as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.
Therefore, consent from the MAH of the Arava application, which was submitted within the scope of Part B of the Annex of the Council Regulation (EEC) 2309/93, of the 22 July 1993, has been given allowing access to Module 2 to Module 5 of the initial dossier of this authorised product and any subsequent post-marketing procedures submitted, assessed and approved. The application for Leflunomide Winthrop consists only of Module 1 information.

As a consequence, quality, safety and efficacy of the Leflunomide Winthrop medicinal product are identical to the up-to-date quality, safety and efficacy profile of Arava. Information on the scientific discussions can be found in the Arava CHMP assessment reports and in the European Public Assessment Report (EPAR).

The approved indication is:

“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 (see section 4.4 of SPC) may also increase the risk of serious adverse reactions even for a long time after the switching.”

The recommended dosage and method of administration are as follows:

Posology

Leflunomide therapy 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 maintenance dose for patients with psoriatic arthritis is 20 mg once daily (see section 5.1 of the SPC).

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

There is no dose adjustment recommended in patients with mild renal insufficiency.

No dosage adjustment is required in patients above 65 years of age.

Paediatric population
Leflunomide Winthrop is not recommended for use in patients below 18 years since efficacy and safety in juvenile rheumatoid arthritis (JRA) have not been established (see sections 5.1 and 5.2 of SPC).

It is noted that treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis and the following monitoring applies:.

Alanine aminotransferase (ALT) or serum glutamopyruvate transferase (SGPT) and a complete blood cell count, including a differential white blood cell count and a platelet count, must be checked simultaneously and with the same frequency:

- before initiation of leflunomide,
- every two weeks during the first six months of treatment, and
- every 8 weeks thereafter (see section 4.4 of SPC).

Leflunomide is a pyrimidine synthesis inhibitor that acts by reversibly blocking the enzyme dihydro-orotate dehydrogenase, resulting in antiproliferative effects.

The clinical benefits of Leflunomide Winthrop are shown by response to treatment, as defined by disease-specific criteria (American College of Rheumatology response rates for rheumatoid arthritis and the Psoriatic Arthritis treatment Response Criteria for psoriatic arthritis). In rheumatoid arthritis, leflunomide was shown to be more effective than placebo and as effective as sulphasalazine. Also, over one year treatment, leflunomide was as effective as methotrexate (+ folate). In psoriatic arthritis, leflunomide was more effective than placebo, with 59% of the patients taking leflunomide responding to treatment, compared with 30% of those taking placebo.

The most common side effects seen with leflunomide are leucopenia, mild allergic reactions, increased creatine phosphokinase levels, paraesthesia, headache, dizziness, mild increases in blood pressure, diarrhoea, nausea, vomiting, inflammation of the mouth such as mouth ulcers, abdominal pain, increased liver enzyme levels, hair loss, eczema, rash, pruritus, dry skin, tenosynovitis, loss of appetite, weight loss and asthenia.

2.2 Quality aspects

Since this application is an informed consent of the Arava application, the quality data in support of the Leflunomide Winthrop application are identical to the up-to-date quality data of the Arava dossier which have been assessed and approved (including all post-marketing procedures).

2.3 Non-clinical aspects

Since this application is an informed consent of the Arava application, the non-clinical data in support of the Leflunomide Winthrop application are identical to the up-to-date non-clinical data of the Arava dossier, which have been assessed and approved (including all post-marketing procedures).

Ecotoxicity/environmental risk assessment

The Applicant refers to the Guideline on the environmental risk assessment of medicinal products for human use (June 2006, EMEA/CHMP/SWP/4447/00). In Chapter 8 it is stated: “There may be cases in which the absence of an ERA could be justified (e.g. marketing authorisation applications for generic medicinal products or type II variations). In these cases, the expert should provide a rationale for the absence of an ERA, taking into consideration a possible significant increase of environmental exposure to the drug substance”. As article 10c of Directive 2001/83/EC applies to medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form, and in this application clinical particulars (indication and dosage) are the same as for the reference product, it is clear that the introduction of Leflunomide Winthrop to the market will only lead to substitution of Arava or other generic leflunomide containing medicinal products. A possible significant increase of environmental exposure is not expected. The environmental exposure is very low.

In order to enhance environmental protection, the proposed package leaflet includes the following general statement: “Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment”.

The absence of an ERA has been justified.

2.4 Clinical aspects

Since this application is an informed consent of the Arava application, the clinical data in support of the Leflunomide Winthrop application are identical to the up-to-date clinical data of the Arava dossier, which have been assessed and approved (including all post-marketing procedures).

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Hepatic reactions	Routine pharmacovigilance Special focus in PSUR	**Labelling** 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 and psoriatic arthritis ([Section 4.2] of SPC). **Communication and Educational Program** to emphasize to prescribers the importance of monitoring liver function.
Blood cytopenia	Routine pharmacovigilance	**Labelling** Contraindication in [Section 4.3] of SPC 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. 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 haematologic 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	**Labelling** 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 multiform) 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	**Labelling** Contraindication in [Section 4.3] of SPC with regard to patients having severe infections. Warning in [Section 4.4] of SPC stating that medications with immunosuppressive properties, like leflunomide, can cause patients to be more susceptible to infections, including opportunistic infections, recommending that treatment with leflunomide be discontinued in the event of severe uncontrolled infections, and that a washout procedure be administered in the event that severe, uncontrolled infections occur. Information in [Section 4.8] of SPC about this risk as an Undesirable effect. **(Restricted distribution** through legal status of prescription). **Communication and Educational Program** to emphasize to prescribers the immunosuppressive 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 focus in PSUR	**Labelling** 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 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 SPC about this risk as an Undesirable event. **(Restricted distribution** through legal status of prescription).
Teratogenicity	Routine pharmacovigilance Special focus in PSUR	**Labelling** 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 (proposal for Arava® as endorsed by the CHMP meeting dated 24 September 2009). **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 and psoriatic arthritis ([Section 4.2] of SPC).
Hypertension	Routine pharmacovigilance	**Labelling** 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).
Interactions with other DMARDs (methotrexate)	Routine pharmacovigilance Special focus in PSUR	**Labelling** 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 and psoriatic 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 foetal toxicity	Routine pharmacovigilance	**Labelling** Warning in [Section 4.4] of SPC stating that male patients should be aware of the possibility of male-mediated foetal 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 counselling for male patients who wish to father a child. **(Restricted distribution** through legal status of prescription).
Lympho-proliferative disorders	Routine pharmacovigilance Special focus in PSUR	**Labelling** 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).
Progressive multifocal leuko-encephalopathy	Routine pharmacovigilance Special focus in PSUR	Signal still under evaluation for its relevance. No information in the SPC. **(Restricted distribution** through legal status of prescription).
Renal failure	Routine pharmacovigilance Special focus 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	**Labelling** 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 biologic DMARDs	Routine pharmacovigilance Special focus in PSUR	There is no specific recommendation about the concomitant use of leflunomide with biologic DMARs in the SPC, however both types of treatment have their prescription restricted to specialists

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

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Leflunomide Winthrop 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 Winthrop.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Recommendation

Since this application is an informed consent of the Arava application, the CHMP considered that the risk-benefit balance of Leflunomide Winthrop was favourable and therefore recommended the granting of the marketing authorisation for the following indication:

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 (see section 4.4) may also increase the risk of serious adverse reactions even for a long time after the switching.