EU Risk Management Plan for Leflunomide medac

RMP version to be assessed as part of this application:	
RMP Version number:	14.0
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Rationale for submitting an updated RMP:	Adaption to reference product Arava®
Summary of significant changes in this RMP:	Alignment of safety concerns with those of the reference product Adaption to GVP V Rev2 format Change of QPPV

Other RMP versions under evaluation:	
RMP Version number:	Not applicable
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EU-/UK-QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the MAH's QPPV. The electronic signature is available on file.

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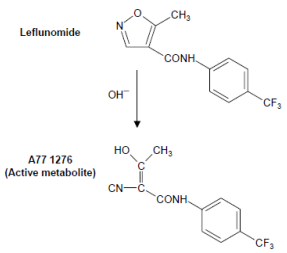
ABBREVIATIONS:

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CEP	Communication and Educational Programme
DMARD	Disease modifying anti-rheumatic drug
DNA	Desoxyribonucleotide acid
eCTD	Electronic Common Technical Document
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
ICSR	Individual Case Safety Reports
INN	International Nonproprietary Name
MAH	Marketing Authorisation Holder
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PsA	Psoriatic arthritis
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Leflunomide
Pharmacotherapeutic group(s) (ATC Code)	L04AK01
Marketing Authorisation (MAH)	medac Gesellschaft für klinische Spezialpräparate mbH Theaterstraße 6 D-22880 Wedel Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Leflunomide medac
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Leflunomide is an isoxazole derivative (Chemical name: N-(4'-trifluoro-methylphenyl)-5-methyl-isoxazole-4-carboxamide; empirical formula: $C_{12}H_9F_3N_2O_2$; molecular weight: 270.2)
	Summary of mode of action: In vivo, leflunomide is rapidly metabolised to its active metabolite A77-1726, the ring-opened form.  The active metabolite of leflunomide inhibits the human enzyme dihydroorotate dehydrogenase. Leflunomide has immunomodulatory/immunosuppressive, antiproliferative, anti-inflammatory properties. In vitro, after mitogen stimulation, A77-1726 inhibits T-cell proliferation, DNA synthesis and expression of certain cell surface and nuclear antigens directly involved in T-cell activation and proliferation. It inhibits mitogen-stimulated proliferation of human peripheral blood mononuclear cells, and

	proliferation in transformed murine and human cell lines, in a dose-dependent fashion.
	Important information about its composition: Not applicable
Hyperlink to the Product Information	eCTD 1.3.1.
Indication(s) in the EEA	Current: Leflunomide is indicated for the treatment of adult patients with: • active rheumatoid arthritis (RA) as a disease-modifying antirheumatic drug (DMARD)active psoriatic arthritis (PsA).
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: *In RA:* Leflunomide therapy is usually started with a loading dose of 100 mg once daily for 3 days. Omission of the loading dose may decrease the risk of adverse events. The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease. *In PsA:* Leflunomide therapy is started with a loading dose of 100 mg once daily for 3 days. The recommended maintenance dose is leflunomide 20 mg once daily.
	Proposed (if applicable): Not applicable
Pharmaceutical form(s) and strengths	Current: Film-coated tablets for oral use Tablet strengths: − Each film-coated tablet contains 10 mg leflunomide − Each film-coated tablet contains 15 mg leflunomide − Each film-coated tablet contains 20 mg leflunomide
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Leflunomide medac is a generic/hybrid product with the reference product being Arava®.

MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

MODULE SIII - CLINICAL TRIAL EXPOSURE

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

MODULE SV - POST-AUTHORISATION EXPERIENCE

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

Leflunomide medac is a generic/hybrid product and therefore this section is not applicable.

MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Hepatic reactions - Blood cytopenia - Infections - Teratogenicity
Important potential risks	- Male-mediated foetal toxicity - Progressive multifocal leukoencephalopathy (PML)
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

The company collects and monitors all spontaneously reported adverse events and commits to a detailed assessment of each report as part of routine pharmacovigilance activities. All events reported to the company or published in the literature will be periodically assessed for trends and PSURs will be provided to the EU regulatory authorities in accordance with the relevant EU Directives.

The company's pharmacovigilance system including routine pharmacovigilance activities is described in its pharmacovigilance system master file (PSMF) and summarised in eCTD Module 1.8.1.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires: None

Other forms of routine pharmacovigilance activities: None

III.2 Additional Pharmacovigilance Activities

None.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

The reference product Arava® has no imposed post-authorisation efficacy studies. According to the GVP guideline, Part IV was therefore omitted.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

The safety information in the product information is aligned to the reference medicinal product Arava®.

Safety concern	Routine risk minimisation activities
Hepatic reactions	**Routine risk communication:** • Labelled in sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the SmPC • Labelled in sections 2 and 4 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for liver function monitoring are included in SmPC section 4.4 • Information on carrying out blood test at regular intervals, before and during treatment with Leflunomide medac to monitor liver in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA.
Blood cytopenia	**Routine risk communication:** • Labelled in sections 4.1, 4.2, 4.3, 4.4 and 4.8 of the SmPC • Labelled in sections 2 and 4 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for a complete blood cell count monitoring are included in SmPC section 4.4 • Information on carrying out blood test at regular intervals, before and during treatment with Leflunomide medac to monitor blood cells in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA.
Infections	**Routine risk communication:** • Labelled in sections 4.3, 4.4 and 4.8 of the SmPC

	• Labelled in sections 2 and 4 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for before treatment active and inactive ("latent") tuberculosis evaluation are included in SmPC section 4.4 • Information on carrying tuberculosis tests before treatment in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA.
Teratogenicity	**Routine risk communication:** • Labelled in sections 4.3 and 4.6 of the SmPC • Labelled in section 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for women of childbearing potential to use effective contraception during and after treatment are included in SmPC section 4.4 • Information on using reliable contraceptive measures in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA.
Male-mediated fetal toxicity	**Routine risk communication**: • Labelled in sections 4.4 and 4.8 of the SmPC • Labelled in section 2 of the PL **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations for male patients to use reliable contraception during treatment are included in the SmPC • Information on using reliable contraceptive measures in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA.
Progressive multifocal leukoencephalopathy	**Routine risk communication:** • Labelled in section 4.4 of the SmPC

(PML)	**Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA.

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Physician Leaflet, Patient Information Sheet and Ad hoc information service are aligned to the reference medicinal product Arava®.

Educational tool for physician (Physician Leaflet)	
Objectives:	To ensure the safe and effective use of leflunomide in the appropriate patient population and reinforce recommendations to the physicians regarding the following risks: hepatic reactions, blood cytopenia, infections, teratogenicity and male-mediated fetal toxicity.
Rationale for the additional risk minimisation activity:	• Compliance with monitoring liver function before starting treatment, every 2 weeks during the first 6 months of treatment and every 8 weeks thereafter. • Compliance with hematologic monitoring before starting treatment, every 2 weeks during the first 6 months of treatment and every 8 weeks thereafter. • Immunosuppressive properties of leflunomide, the risk of infections including opportunistic infections and the contraindication for use in immunocompromised patients and in patients with severe infections. • Recommendation to patient to avoid pregnancy until leflunomide levels are at an appropriate level. • Recommendation to ensure compliance with contraception of male patients selected for leflunomide therapy with regard to the risk of male-mediated fetal toxicity. • Caution to be exercised when combining with other DMARDs.
Target audience and planned distribution path:	Educational support for physicians (Physician Leaflet) The Physician Leaflet, endorsed by the Competent Authority, is provided to the targeted physicians through the appropriate means and channels of communication according to country, and is available by the most appropriate option that may include electronic channels (i.e., website, email)
Plans to evaluate the effectiveness of the interventions and criteria for success:	Routine Pharmacovigilance activities
Educational tool for patients (Patient Information Sheet)	
Objectives:	To ensure the safe and effective use of leflunomide in the appropriate patient population and reinforce recommendations to the patients regarding the risks of teratogenicity and male-mediated fetal toxicity focusing on the recommendation to men wishing the be a father to wait and to female patients to avoid pregnancy until leflunomide levels are at appropriate level.
Rationale for the additional risk	Recommendation to patients to avoid pregnancy until leflunomide levels are at an appropriate level; and to ensure compliance with contraception of male

minimisation activity:	patients selected for leflunomide therapy with regard to the risk of male-mediated fetal toxicity.
Target audience and planned distribution path:	The Patient Information Sheet is to be communicated to patients by their treating physician.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Routine Pharmacovigilance activities.
Ad hoc information service	
Objectives:	To provide additional information on the testing of plasma leflunomide levels.
Rationale for the additional risk minimisation activity:	To ensure plasma leflunomide levels are at appropriate level (target concentration below 0.02 mg/L), recommendation to monitor plasma leflunomide levels at the end of the waiting period or the washout procedure and again after an interval of at least 14 days in female patients and providing additional information on the testing of plasma leflunomide levels after stopping treatment and performing the washout procedure for men wishing to be a father.
Target audience and planned distribution path:	The ad hoc information (through Physician Leaflet) for the testing of plasma leflunomide levels, endorsed by the Competent Authority, is provide to the targeted physicians through the appropriate means and channels of communication according to country, and is available by the most appropriate option that may include electronic channels (i.e., website, email).
Plans to evaluate the effectiveness of the interventions and criteria for success:	Routine Pharmacovigilance activities.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

The safety information in the product information and the additional risk minimisation measures are aligned to the reference medicinal product Arava®.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatic reaction	**Routine risk minimisation measures:** • SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Recommendations for liver function monitoring in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** Educational tool for physicians	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Blood cytopenia	**Routine risk minimisation measures:** • SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Recommendations for a complete blood cell count monitoring in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** Educational tool for physicians	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Infections	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Recommendations for tuberculosis evaluation in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** Educational tool for physicians	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Teratogenicity	**Routine risk minimisation measures:** • SmPC sections 4.3 and 4.6 • PL section 2 • Recommendations for women of childbearing potential to use effective contraception in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** • Educational tool for physicians • Ad hoc information service for the testing of plasma leflunomide levels	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Male-mediated foetal toxicity	**Routine risk minimisation measures:** • SmPC sections 4.4 and 4.8 • PL section 2 • Recommendations male patients to use reliable contraception in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** • Educational tool for physicians • Ad hoc information service for the testing of plasma leflunomide levels	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimisation measures:** • SmPC section 4.4 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Leflunomide medac (leflunomide)

This is a summary of the risk management plan (RMP) for Leflunomide medac. The RMP details important risks of Leflunomide medac, how these risks can be minimised, and how more information will be obtained about Leflunomide medac's risks and uncertainties (missing information).

Leflunomide medac's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Leflunomide medac should be used.

This summary of the RMP for Leflunomide medac should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Leflunomide medac's RMP.

I. The medicine and what it is used for

Leflunomide medac is authorised for the treatment of adult patients with active rheumatoid arthritis (RA) and with active psoriatic arthritis (PsA) (see SmPC for the full indication). It contains leflunomide as the active substance and it is given orally.

Further information about the evaluation of Leflunomide medac's benefits can be found in Leflunomide medac's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/leflunomide-medac.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Leflunomide medac, together with measures to minimise such risks and the proposed studies for learning more about Leflunomide medac's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Leflunomide medac, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Leflunomide medac are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Leflunomide medac. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Summary of safety concerns	
Important identified risks	- Hepatic reactions - Blood cytopenia - Infections - Teratogenicity
Important potential risks	- Male-mediated foetal toxicity - Progressive multifocal leukoencephalopathy (PML)
Missing information	None

II.B Summary of important risks

The safety information in the product information and the additional risk minimisation measures are aligned to the reference medicinal product Arava®.

Important identified risk: Hepatic reaction	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Recommendations for liver function monitoring in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** Educational tool for physicians

Important identified risk: Blood cytopenia	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Recommendations for a complete blood cell count monitoring in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** Educational tool for physicians

Important identified risk: Infections	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 • Recommendations for tuberculosis evaluation in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** Educational tool for physicians

Important identified risk: Teratogenicity	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3 and 4.6 • PL section 2 • Recommendations for women of childbearing potential to use effective contraception in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** • Educational tool for physicians and patients • Ad hoc information service for the testing of plasma leflunomide levels

Important potential risk: Male-mediated foetal toxicity	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC sections 4.3 and 4.6 • PL section 2 • Recommendations for women of childbearing potential to use effective contraception in SmPC section 4.4 and PL section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** • Educational tool for physicians • Ad hoc information service for the testing of plasma leflunomide levels

Important potential risk: Progressive multifocal leukoencephalopathy (PML)	
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC section 4.4 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA. **Additional risk minimisation measures:** None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Leflunomide medac.

II.C.2 Other studies in the post-authorisation development plan

There are no studies required for Leflunomide medac.

PART VII: ANNEXES

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ANNEX 1 - EUDRAVIGILANCE INTERFACE

Not applicable

ANNEX 2 - TABULATED SUMMARY OF PLANNED, ON-GOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Not applicable.

ANNEX 3 - PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Not applicable.

ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 5 - PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Not applicable.

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Additional risk minimisation measures include educational tools for physician and patient, and an ad hoc information service. The educational tools comprises of Physician Leaflet and Patient Information Sheet covering four safety concerns (hepatic reactions, blood cytopenia, infections, teratogenicity) for which routine minimisation activity through labeling is considered not sufficient.
The ad hoc information service is designed to address the risks of teratogenicity and male mediated foetal toxicity by providing additional information on the testing of plasma leflunomide levels after stopping treatment and performing the wash out procedure for women wishing to be pregnant or for men wishing to be a father.

Approved key messages of the additional risk minimisation measures

1. **Educational tools for physicians:**
   - Physician Leaflet
     - Relevant information of the safety concern(s) addressed by the aRMM
       The most important risks you should be aware of when prescribing Leflunomide medac include:
       - Risk of hepatotoxicity, including very rare cases of severe liver injury, which may be fatal
       - Risk of haematotoxicity, including rare cases of pancytopenia, leucopenia, eosinophilia and very rare cases of agranulocytosis
       - Risks of infections including rare cases of severe uncontrolled infections (sepsis), which maybe fatal
       - Risk of serious birth defects when administered during pregnancy

     - Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management
       - Routine blood monitoring:
         - Due to the risk of hepato- and haematoxicity, which in rare cases can be severe or even fatal, a careful monitoring of hepatic parameters and blood cell count before and during treatment with Leflunomide medac is essential.
         - More information about the occurrence of these adverse effects is available in the Summary of Product Characteristics.

Concomitant administration of Leflunomide medac and hepatotoxic or haematotoxic DMARDs (e.g., methotrexate) is not advisable.

- Key message to convey in patients counselling
  - Before starting the treatment with Leflunomide medac, please ensure that patients have been counselled on important risks associated with leflunomide therapy and appropriate precautions to minimise these risks. To this aim, a specific Patient Leaflet has been developed by the Marketing Authorisation Holder (MAH) in addition to the present safety information sheet.

- Instructions on how to handle possible adverse events
  - Infections: Leflunomide medac immunosuppressive properties may cause patients to be more susceptible to infections, including opportunistic infections, and may rarely cause severe uncontrolled infections (e.g., sepsis) as well as infections severe in nature, such as Progressive Multifocal Leukoencephalopathy (PML).
  - Patients with tuberculin reactivity must be carefully monitored because of the risk of tuberculosis.
  - In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a wash-out procedure (see section "Wash-out procedure").
  - Leflunomide medac is contraindicated in:
    - Patients with severe immunodeficiency states, e.g., AIDS
    - Patients with serious infections

- Pregnancy: Please inform the women of childbearing potential, women who wish to become pregnant and men wishing to father a child, about the risk of birth defects with Leflunomide medac and the necessity to use reliable contraception. Please also discuss the measures to follow in case of inadvertent pregnancy during treatment and after treatment's discontinuation. This information should be given before treatment, regularly during treatment and after treatment.

  - Risk on birth defects. Based on animal studies, the active metabolite of leflunomide A771726 is suspected to cause serious birth defects when administered during pregnancy. Therefore Leflunomide medac is contraindicated in pregnancy.

  - Women
    - Wash-out procedure: Start the wash-out procedure which allows avoiding the 2-year waiting period. Both colestyramine and activated powdered charcoal

are able to modify the absorption of oestrogens and progestrogens, therefore use of alternative contraceptive methods other than oral contraceptives is recommended during the entire wash-out period.

If the wash-out procedure cannot be performed, a 2-year waiting period under reliable contraception is required after treatment discontinuation before becoming pregnant.

- Testing at the end of the wash-out period: Two separate tests at an interval of at least 14 days must be performed.
  - If the 2 test results are <0.02 mg/L (0.02 µg/mL), no further procedures are necessary. A waiting period of one-and-a half months between the first result <0.02 mg/L and fertilisation is required.
  - If results of either test are >0.02 mg/L (0.02 µg/mL), the washout procedure must be performed again, with 2 separate tests at 14 days of interval.
  - Between the first occurrence of a plasma concentration below 0.02 mg/L and fertilisation, a waiting period of one-and-a-half months is required.

- Men:
As there is a possible male-mediated foetal toxicity, reliable contraception during treatment with Leflunomide medac should be guaranteed.
  - For men wishing to father a child, the same wash-out procedure as recommended for women should be considered.
  - Between the first occurrence of a plasma concentration below 0.02 mg/L and fertilisation, a waiting period of 3 months is required.

- Ad hoc advisory service: An ad hoc advisory service is available for providing information on leflunomide plasma level testing for patients treated with Leflunomide medac.

- Wash-out procedure: Plasma levels of the active metabolite of leflunomide, A771726 can be expected to be above 0.02 mg/L for a prolonged period. The concentration may be expected to decrease below 0.02 mg/L about 2 years after stopping the treatment with Leflunomide medac.
- The wash-out procedure is recommended to accelerate A 771726 elimination, when its needs to be cleared rapidly from the body.

2. Educational tools for patients

- Patient Information Sheet
  - Leflunomide medac may increase the risk of serious birth defects

    You may be at increased risk of having a baby with a birth defect if:
    - You are pregnant when you start taking Leflunomide medac, or
    - You become pregnant while you are taking Leflunomide medac, or
    - You do not wait to become pregnant until you have stopped taking Leflunomide medac and followed the drug wash-out procedure described below, or
    - You become pregnant within 2-years after you stopped Leflunomide medac

  - Precautions of use for Leflunomide medac

    If you are a woman of childbearing potential, you and your partner should take every precaution to avoid becoming pregnant, such as both partners using reliable birth control as recommended by your doctor when:
    - You are currently taking Leflunomide medac, or
    - You have discontinued Leflunomide medac and are going through the drug wash-out procedure, or
    - You have discontinued Leflunomide medac less than 2 years ago

    It is VERY IMPORTANT that you contact your doctor IMMEDIATELY if your menstrual period is at all late or if for any other reason you believe you may be pregnant.

  - Leflunomide medac wash-out procedure

    After discontinuing Leflunomide medac, your doctor will order you a drug wash-out procedure. The aim of this procedure is to remove the drug rapidly and sufficiently from your body. The wash-out procedure consists of a full 11-day course of certain drugs which speed up the removal of Leflunomide medac, from your body. This course is followed by 2 separate laboratory blood tests at least 14 days apart to assure a very low drug level in your body. If your leflunomide levels are still too high, a repeated drug wash-out procedure may be necessary.

    When it is confirmed that leflunomide has been sufficiently removed from your body by the 2 separate laboratory blood tests, you should then wait for at least another month before you become pregnant.

    If you do not follow the drug wash-out procedure, it could take up to 2 years to reach this very low drug level in your blood.

If you are a man wishing to be a father

As it cannot be excluded that leflunomide passes into semen, reliable contraception during treatment with Leflunomide medac should be guaranteed.

When you want to father a child, you should discuss with your doctor who could advise you stop Leflunomide medac and then undergo the drug wash-out procedure (as described above).

When it is confirmed that Leflunomide medac has been sufficiently removed from your body, men should then wait for at least 3 months before fertilisation.

For further information, please contact your doctor.

ANNEX 7 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

None

ANNEX 8 - SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date Procedure	Change
6	EU/1/10/637/001-013	Safety concerns Progressive Multifocal Leukoencephalopathy reclassified from important identified risk to important potential risk
7	EU/1/10/637/001-013	Safety concerns Peripheral neuropathy added as new important potential risk
8	EU/1/10/637/001-013	Other Adaptation of Version 7 to the newest format of RMPs as published on the EMA website. Inclusion of the new indication "Psoriatic arthritis"
9	EU/1/10/637/001-013	Other The new indication "psoriatic arthritis" required a change of the Educational Material (distribution not restricted to rheumatologists; it has to be send to all physicians who are expected to prescribe/use the product).
10	EU/1/10/637/001-013	Safety concerns Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) added as new important identified risk
11	EU/1/10/637/001-013	Other The changes of Part VI and Annex 10 made in RMP version 9 were not accepted by EMA and therefore deleted.
12	EU/1/10/637/001-013	Safety concerns DRESS included as important identified risk under the heading 'Severe skin reactions'
13	22/01/2015 EMEA/H/C/001227/R/0019	Safety concerns Interaction with other DMARDs (methotrexate) rephrased to "Concomitant use of other DMARDs (methotrexate)" to be in line with the originator Risk of interaction with CYP2C8 substrates, CYP1A2 substrates, BCRP substrates, OATP1B1/B3 substrates, OAT3 substrates, warfarin and oral contraceptiva

14.0	Submitted within a variation to adapt the safety concerns to reference product Arava®	Safety concerns Alignment of safety concerns with those of the reference product Arava®: Important identified risks removed: - Severe skin reactions - Interstitial lung disease - Hypertension - Concomitant use of other DMARDs (e.g. methotrexate) Important potential risks removed: - Lymphoproliferative disorders - Renal failure - Peripheral neuropathy - Risk of interaction with CYP2C8 substrates, CYP1A2 substrates, BCRP substrates, OATP1B1/B3 substrates, OAT3 substrates, warfarin and oral contraceptiva Missing information removed: - Use in children - Concomitant use of biologic DMARDs Other Adaptation to GVP V Rev2 format Change of QPPV