EU RISK MANAGEMENT PLAN

LEFLUNOMIDE

RMP version to be assessed as part of this application	
RMP version number	4.0
Data lock point for this RMP	30 November 2024
Date of final sign off	17 December 2024
Rationale for submitting an updated RMP	RMP v4.0 prepared: • To update the list of safety concerns and details of ARMMs in line with innovator's (Arava®, Sanofi-aventis) RMP v5.1; • RMP document prepared based on the new Guidance on the format of the risk management plan (RMP) in the EU (Revision 2.0.1, dated 31 October 2018).

QPPV Details	
QPPV name:	Iva Novak
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV/deputy. The signature is available on file.

Table 1: Summary of Significant Changes in This RMP Version

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part I Product(s) overview	3.2 (23 April 2015)	Update of administrative data. ATC code updated to dihydroorotate dehydrogenase (DHODH) inhibitors (L04AK01). Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements.
Part II - Module SI Epidemiology of the indication(s) and target population(s)	Not applicable.	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements
Part II - Module SII Non-clinical part of the safety specification	Not applicable.	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements
Part II - Module SIII Clinical trial exposure	Not applicable.	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements
Part II - Module SIV Populations not studied in clinical trials	Not applicable.	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements
Part II - Module SV Post-authorisation experience	3.2 (23 April 2015)	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements
Part II - Module SVI Additional EU requirements for the safety specification	Not applicable.	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements
Part II - Module SVII Identified and potential risks	3.2 (23 April 2015)	Section revised to: • Reflect changes introduced to the list of safety concerns in line with innovator's (Arava®, Sanofi-aventis) RMP v5.1; • Present data according to the GVP Module V Revision 2.0.1 RMP template requirements.
Part II - Module SVIII Summary of the safety concerns	3.2 (23 April 2015)	List of safety concerns aligned with reference medical product's (Arava®, Sanofi-aventis) RMP v5.1. Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements.

RMP part/module	Part/module version number and date of approval (opinion date)	High level description of major changes
Part III Pharmacovigilance plan (including post-authorisation safety studies)	3.2 (23 April 2015)	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements.
Part IV Plans for post-authorisation efficacy studies	3.2 (23 April 2015)	Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements.
Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	3.2 (23 April 2015)	Section revised to: • Reflect changes in the list of safety concerns introduced in line with innovator's (Arava®, Sanofi-aventis) RMP v5.1; • Details of additional risk minimisation measures (ARMMs) aligned with Arava®'s RMP v5.1; • Present data according to the GVP Module V Revision 2.0.1 RMP template requirements.
Part VI Summary of the risk management plan	3.2 (23 April 2015)	Section revised to: • Reflect changes in the list of safety concerns introduced in line with innovator's (Arava®, Sanofi-aventis) RMP v5.1; • Present data according to the GVP Module V Revision 2.0.1 RMP template requirements.
Part VII Annexes	3.2 (23 April 2015)	Annex 6: ARMM key messages aligned with Arava®'s (Sanofi-aventis) RMP v5.1; Annex 8 added to reflect changes introduced to the RMP v4.0. Section revised to present data according to the GVP Module V Revision 2.0.1 RMP template requirements.

Details of the currently approved RMP	
Version number	3.2
Approved with procedure	EMEA/H/C/002035
Date of approval (opinion date)	23 April 2015

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ARMM	Additional Risk Minimisation Measure
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CNS	Central Nervous System
CTD	Common Technical Document
e.g.	example given
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GVP	Good Pharmacovigilance Practices
HIV	Human Immunodeficiency Virus
i.e.	Id est (engl.: that means)
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
MAH	Marketing Authorisation Holder
PL	Package Leaflet
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary Of Product Characteristics

Part I: Product(s) Overview

Table 2: Product(s) Overview

Active substance(s) (INN or common name)	**Leflunomide**
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, dihydroorotate dehydrogenase (DHODH) inhibitors (L04AK01)
Marketing Authorisation Holder/Applicant	Ratiopharm GmbH Graf-Arco-Straße 3, 89079 Ulm Germany
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	[Leflunomide ratiopharm] 10 mg and 20 mg film-coated tablets
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: Leflunomide is an isoxazole derivative (chemical name: α,α,α-Trifluoro-5-methyl-4-isoxazolecarboxy-p-toluidide) that inhibits pyrimidine synthesis.
	Summary of mode of action: Leflunomide inhibits human dihydroorotate dehydrogenase (DHODH), an enzyme required for the de novo biosynthesis of pyrimidines and, therefore, of DNA and RNA. Anti-inflammatory effects have been demonstrated in in vivo and in vitro experimental models. In addition, leflunomide has antiproliferative activity.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to CTD Module 1.3.1.
Indication(s) in the EEA	**Current**: Leflunomide is indicated for the treatment of adult patients with: • active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD). • active psoriatic arthritis.
	Proposed (if applicable): Not applicable.

Dosage in the EEA	**Current**: The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis. Posology • In rheumatoid arthritis: 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 psoriatic arthritis: 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. The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	**Current**: 10 mg and 20 mg film-coated tablets
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Not applicable.

Part II: Module SII - Non-Clinical Part of the Safety Specification

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable.

Part II: Module SIV - Populations Not Studied in Clinical Trials

Not applicable.

Part II: Module SV - Post-Authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

This section is not applicable as the previously approved version of the RMP is v3.2.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

The safety concerns in leflunomide EU-RMP v3.2 (signed on 13 March 2015; approved on 23 April 2015), prepared in line with GVP Module V Rev.1 requirements, were defined as follows:

Table 3: Summary of Safety Concerns in Leflunomide EU-RMP v3.2 (approved on 23 April 2015)

Summary of safety concerns	
Important identified risks	• Hepatic reactions • Blood cytopenia • Immunosupressive effects/Infections • Interstitial lung disease • Teratogenicity • Hypertension • Concomitant use of other Disease-modifying antirheumatic drug (DMARDs) (methotrexate)
Important potential risks	• Male-mediated fetal toxicity • Lymphoproliferative disorders • Progressive multifocal leukoencephalopathy (PML) • Renal failure • Peripheral neuropathy • Risk of interaction (with CYP2C8 substrates, CYP1A2 substrates, BCRP substrates, OATP1B1/B3 substrates, OAT3 substrates, warfarin and oral contraceptives)
Missing information	• Use in children • Concomitant use of biologic DMARDs

In leflunomide RMP **v4.0**, the following safety concerns were removed from the list of safety concerns or renamed:

Removed safety concerns:

<u>Important identified risks</u>:

- Severe skin reactions
- Interstitial lung disease
- Hypertension
- Concomitant use of other Disease-modifying antirheumatic drugs (DMARDs) (methotrexate)

<u>Important potential risks</u>:

- Lymphoproliferative disorders
- Renal failure

- Peripheral neuropathy
- Risk of interaction (with CYP2C8 substrates, CYP1A2 substrates, BCRP substrates, OATP1B1/B3 substrates, OAT3 substrates, warfarin and oral contraceptives)

Missing information:

- Use in children
- Concomitant use of biologic DMARDs

Renamed safety concern:

- Important identified risk ‘Immunosuppressive effects/infections’ was renamed to ‘Infections’.

Rationale for the removal and renaming of Important Identified Risks, Important Potential Risks, and Missing information from the list of safety concerns in RMP v4.0:

Specific safety concerns were renamed or removed from the summary of safety concerns in RMP v4.0 in line with the list of safety concerns in innovator’s (Arava®, Sanofi-aventis) EU RMP v5.1 published on European public assessment report (EPAR) on 09 March 2023.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 4: Summary of Safety Concerns

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

The summary of safety concerns is aligned with the list of safety concerns in the innovator's (Arava®, Sanofi-aventis) EU RMP v5.1 published on European public assessment report (EPAR) on 09 March 2023.

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Specific adverse reaction follow-up questionnaires:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Not applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-Authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

V.1. Routine Risk Minimisation Measures

Table 5: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation measures
IMPORTANT IDENTIFIED RISKS	
Hepatic reactions	**Routine risk communication:** Risk is listed in SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.8. Described in PL sections 2 and 4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** Recommendation for liver function monitoring is included in SmPC section 4.4. Recommendation on carrying out blood tests at regular intervals, before and during treatment with leflunomide, to monitor the liver in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.
Blood cytopenia	**Routine risk communication:** Risk is listed in SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.8. Described in PL sections 2 and 4. **Routine risk minimisation measures 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 tests at regular intervals, before and during treatment with leflunomide, to monitor the blood cells in PL section 2 **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.
Infections	**Routine risk communication:** Risk is listed in SmPC sections 4.3, 4.4, and 4.8. Described in PL sections 2 and 4. **Routine risk minimisation measures 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 out tuberculosis tests before treatment in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.
Teratogenicity	**Routine risk communication:** Risk is addressed in SmPC sections 4.3 and 4.6. Described in PL section 2.

Safety concern	Routine risk minimisation measures
	Routine risk minimisation measures recommending specific clinical measures to address the risk: Recommendation for woman of childbearing potential to use effective contraception during and up to 2 years after treatment is included in SmPC sectionand 4.6. Information on using reliable contraceptive measures in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.
IMPORTANT POTENTIAL RISKS	
Male-mediated fetal toxicity	**Routine risk communication:** Risk is listed in SmPC sections 4.4 and 4.8. Described in PL section 2. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** Recommendations for male patients to use reliable contraception during 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:** Prescription only medicine. The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.
Progressive multifocal leukoencephalopathy (PML)	**Routine risk communication:** Risk is addressed in SmPC section 4.4. **Routine risk minimisation measures recommending specific clinical measures to address the risk:** None**.** **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. The treatment should be initiated and supervised by specialists experienced in the treatment of rheumatoid arthritis and psoriatic arthritis.

V.2. Additional Risk Minimisation Measures

Table 6: Educational tool for physicians (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 patients 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). Prior to the launch of the medical product in each Member State the Marketing Authorisation Holder (MAH) agrees about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority in each country.
Plans to evaluate the effectiveness of the interventions and criteria for success	The success of proposed additional risk minimization activities will be measured by: • monitoring dissemination coverage – risk minimization tool implementation. The implementation will be considered successful if MAH fulfilled obligation(s). • potential occurrence in the relevant cases. The ARMMs will be considered successful if no significant occurrence in the period after ARMMs implementation, without an alternative explanation, is noticed. Results of effectiveness evaluation will be presented in periodic reports.

Table 7: 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 risk of teratogenicity and male-mediated fetal toxicity focusing on the recommendation to men wishing to be a father to wait and to female patients to avoid pregnancy until leflunomide levels are at an appropriate level.
Rationale for the additional risk minimisation activity	Recommendation to patients to avoid pregnancy until leflunomide levels are at an appropriate level; and to ensure compliance with contraception of male patients selected for leflunomide therapy with regards 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. Prior to the launch of the medical product in each Member State the MAH agrees about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority in each country.
Plans to evaluate the effectiveness of the interventions and criteria for success	The success of proposed additional risk minimization activities will be measured by: • monitoringdissemination coveargе– risk minimization tool implementation. The implementation will be considered successful if MAH fulfilled obligation(s). • potential occurrence in the relevant cases. The ARMMs will be considered successful if no significant occurrence in the period after ARMMs implementation, without an alternative explanation, is noticed.

	Results of effectiveness evaluation will be presented in periodic reports.

Table 8: 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 an 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 for the testing of plasma leflunomide levels is provided to the target physicians through Physician Leaflet and SmPC. Prior to the launch of the medical product in each Member State the MAH agrees about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority in each country.
Plans to evaluate the effectiveness of the interventions and criteria for success	The success of proposed additional risk minimization activities will be measured by: • monitoring dissemination coverage – risk minimization tool implementation. The implementation will be considered successful if MAH fulfilled obligation(s). • potential occurrence in the relevant cases. The ARMMs will be considered successful if no significant occurrence in the period after ARMMs implementation, without an alternative explanation, is noticed. Results of effectiveness evaluation will be presented in periodic reports.

V.3. Summary of Risk Minimisation Measures

Table 9: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
IMPORTANT IDENTIFIED RISKS		
Hepatic reactions	**Routine risk minimisation measures:** SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.8. PL sections 2 and 4. Recommendation for liver function monitoring is included in SmPC section 4.4. and PL section 2. Prescription only medicine. **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
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 are included in SmPC section 4.4 and PL section 2. Prescription only medicine. **Additional risk minimisation measures:** Educational tool for physicians.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Infections	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8. PL sections 2 and 4. Recommendations for tuberculosis evaluation are included in SmPC section 4.4 and PL section 2. Prescription only medicine. **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 are included in SmPC section 4.6 and PL section 2. Prescription only medicine. **Additional risk minimisation measures:** Educational tool for physicians. Educational tool for patients. 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.
IMPORTANT POTENTIAL RISKS		
Male-mediate fetal toxicity	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8. PL section 2. Recommendation for male patients to use reliable contraception during treatment are included in SmPC section 4.4 and PL section 2. Prescription only medicine. **Additional risk minimisation measures:** Educational tool for physicians. Educational tool for patients. 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
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimisation measures:** SmPC sections 4.4. Prescription only medicine. **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 RATIOPHARM 10 mg and 20 mg film-coated tablets

This is a summary of the risk management plan (RMP) for LEFLUNOMIDE 10 mg and 20 mg film-coated tablets (hereinafter referred to as Leflunomide). The RMP details important risks of Leflunomide, how these risks can be minimised, and how more information will be obtained about Leflunomide's risks and uncertainties (missing information).

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

This summary of the RMP for Leflunomide 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's RMP.

I. The Medicine and What It is used for

Leflunomide is authorised for the treatment of adult patients with:

- active rheumatoid arthritis as a “disease-modifying antirhematic drug” (DMARD)
- active psoriatic arthritis (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’s benefits can be found in Leflunomide’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-ratiopharm

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Leflunomide together with measures to minimise such risks and the proposed studies for learning more about Leflunomide'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, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 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. 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).

Table 10: Summary of Safety Concerns

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

II.B Summary of Important Risks

Table 11: Summary of Pharmacovigilance Activities and Additional Risk Minimisation Activities by Safety Concern

Important identified risk: Hepatic reactions	
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. Recommendation for liver function monitoring is included in SmPC section 4.4. and PL section 2. Prescription only medicine. 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 are included in SmPC section 4.4 and PL section 2.

	Prescription only medicine. 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 are included in SmPC section 4.4 and PL section 2. Prescription only medicine. 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 are included in SmPC section 4.6 and PL section 2. Prescription only medicine. Additional risk minimisation measures Educational tool for physicians. Educational tool for patients. Ad hoc information service for the testing of plasma leflunomide levels.
Important potential risk: Male-mediated fetal toxicity	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 and 4.8. PL section 2. Recommendation for male patients to use reliable contraception during treatment are included in SmPC section 4.4 and PL section 2. Prescription only medicine. Additional risk minimisation measures Educational tool for physicians. Educational tool for patients. 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 sections 4.4. Prescription only medicine. 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.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Leflunomide.

Part VII: ANNEXES

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Annex 4 – Specific Adverse Drug Reaction Follow-Up Forms

Not applicable.

Annex 6 – Details of Proposed Additional Risk Minimisation Activities (if Applicable)

Additional risk minimization measures include Educational tools for physician and patient, and an ad hoc information service. The educational tools comprise of Physician Leaflet and Patient Information Sheet covering four safety concerns (hepatic reactions, blood cytopenia, infections, teratogenicity) for which routine minimization activity through labeling is considered not sufficient. The ad hoc information service is designed to address the risks of teratogenicity and male mediated fetal 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 minimization measures

1. **Educational tools for Physician:**
   - Physician Leaflet

1.1 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 include:

  - Risk of hepatotoxicity, including very rare cases of severe liver injury, which may be fatal
  - Risk of hematotoxicity, 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 may be fatal
  - Risk of serious birth defects when administered during pregnancy

- Details on how to minimize the safety concern addressed by the aRMM through appropriate monitoring and management
  - Routine blood monitoring:
    - Due to the risk of hepato- and hematoxicity, 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 is essential.
    - More information about the occurrence of these adverse effects is available in the Summary of Product Characteristics.

    Concomitant administration of leflunomide and hepatotoxic or hematotoxic DMARDs (eg, methotrexate) is not advisable.

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

- Instructions on how to handle possible adverse events
  - Infections: leflunomide immunosuppressive properties may cause patients to be more susceptible to infections, including opportunistic infections, and may rarely cause severe uncontrolled infections (eg, 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 is contraindicated in:
    - Patients with severe immunodeficiency states, eg, 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 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 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/Land fertilization is required.

      ~ If results of either test are >0.02 mg/L (0.02 µg/mL), the wash-out 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 fertilization, 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 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 fertilization, 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. Please contact Teva Group company to obtain further information concerning this service (Internal note: local contact details to be added).

- 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.
- The wash-out procedure is recommended to accelerate A771726 elimination, when it needs to be cleared rapidly from the body.

2. Educational tool for Patient:

- Patient Information Sheet

2.1 Patient Information Sheet:

- Leflunomide 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, or
- You become pregnant while you are taking leflunomide, or
- You do not wait to become pregnant until you have stopped taking leflunomide and followed the drug wash-out procedure described below, or
- You become pregnant within 2-years after you stopped leflunomide

- Precautions of use for leflunomide

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, or
- You have discontinued leflunomide and are going through the drug wash-out procedure, or
- You have discontinued leflunomide 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 wash-out procedure

After discontinuing leflunomide, 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 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 should be guaranteed.

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

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

For further information, please contact your doctor.