Risk Management Plan for Leflunomide

No 42/23

RMP version to be assessed as part of this application:

RMP Version number:	V 4.1	
Data lock point for this RMP:	28 August 2023	
Date of final sign off:	Please see QPPV signature. Sign off date is part of electronic signature.	
Rationale for submitting an updated RMP:	Alignment with the new EU template (GVP Module V Rev. 2). Harmonisation of the RMP with the reference product.	
Summary of significant changes in this RMP:	Part II: Module SVIII Summary of the Safety Concerns	Harmonisation of the list of safety concerns with the reference product.
	Part VII: Annexes	Addition of the summary table in Annex 8.
Other RMP versions under evaluation:	RMP version number:	Not applicable
	Submitted on:	Not applicable
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Details of the currently approved RMP:	RMP version number:	4.0
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QPPV name:	Ludmila FILIPOVÁ, MD	
QPPV (or delegate) signature:	*The electronic signature is available on file.* *Sign-off date 29 September 2023.*	
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ZENTIVA

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List of Abbreviations

ATC	Anatomical Therapeutic Chemical classification
DMARD	Disease Modifying Antirheumatic Drug
eCTD	Electronic Common Technical Document
INN	International Nonproprietary Name
MAA	Marketing Authorisation Applicant
MAH	Marketing Authorisation Holder
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PsA	Psoriatic Arthritis
PSUR	Periodic Safety Update Report
RA	Rheumatoid arthritis
RMP	Risk Management Plan
QPPV	Qualified Person for Pharmacovigilance
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)	Selective immunosuppressants, ATC code: L04AA13
Marketing Authorisation Holder/Applicant	Zentiva k.s.
Medicinal products to which this RMP refers	3
Invented name(s)	Leflunomide Zentiva
Marketing authorisation procedure	Centralised procedure EMEA/H/C/001129
Brief description of the product	Chemical class: Leflunomide is an isoxazole derivative. Leflunomide is a prodrug: in vivo, leflunomide is immediately metabolized to its active metabolite A771726, the ring-opened form.
	Summary of mode of action: Leflunomide has immunomodulating/immunosuppressive characteristics, acts as an antiproliferative agent, and displays anti-inflammatory properties. In vitro, after mitogen stimulation, A771726 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: None.
Hyperlink to the Product Information	Please refer to section 1.3.1 in eCTD.
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. Recent or concurrent treatment with hepatotoxic or hematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects. Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching.
	Proposed (if applicable): Not applicable.
Dosage in the EEA	Current:

	Treatment with leflunomide should be initiated and supervised by specialists experienced in the treatment of rheumatoid and psoriatic arthritis. **In rheumatoid arthritis:** leflunomide therapy is usually started with a loading dose of 100 mg once daily for three 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 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 after the start of treatment. *For further details please refer to section 1.3.1 in eCTD.*
	Proposed (if applicable): Not applicable.
Pharmaceutical form(s) and strengths	Current: Leflunomide 10 mg film-coated tablets Leflunomide 20 mg film-coated tablets Leflunomide 100 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)

The indications and target population is identical with the reference medicinal product Arava (Sanofi-Aventis), therefore the epidemiology of the indication(s) and target population(s) is also considered to be identical. The chapter is therefore considered not applicable.

Part II: Module SII - Non-clinical part of the safety specification

Please refer to section 2.4 in eCTD (Non-clinical Overview) and RMP part II: Module SII of the reference medicinal product Arava. The MAH does not own its data.

Part II: Module SIII - Clinical trial exposure

MAH hasn't performed any clinical trial. Please refer to section 2.5 in eCTD (Clinical Overview) and RMP part II: Module SIII of the reference medicinal product Arava. The MAH does not own its data.

Part II: Module SIV - Populations not studied in clinical trials

MAH hasn't performed any clinical trial. Please refer to section 2.5 in eCTD (Clinical Overview) and RMP part II: Module SIV of the reference medicinal product Arava. The MAH does not own its data.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Internal database was used as the source for sales data retrieval. The system collects data on yearly and monthly basis.

SV.1.2 Exposure

Leflunomide registered via EMEA/H/C/001129 is marketed in 12 countries [redacted]

The patient exposure is calculated using the WHO Defined Daily Dose (DDD) for leflunomide: 20 mg.

Based on sales data available between Jan-2010 and Jul-2023, 319 230 of 20 mg tablets, 76 380 of 10 mg tablets, 10 095 of 100 film-coated tablets, 28 981 351 of 10 mg film-coated tablets and 87 380 046 of 20 mg film-coated tablets and a total of **116 767 102** tablets of leflunomide were sold. These represent **102 230 161** patient-treatment-days (corresponding to **280 082** patient-treatment-years).

Table SV.1: Exposure table by indication, < gender >, < age group >, < region >

Specific patient exposure data by indication, gender, age group, region or other relevant parameters are not available.

Part II: Module SVI - Additional requirements for the safety specification

Potential for misuse for illegal purposes

Non-clinical and clinical data, as well as postmarketing experience, do not demonstrate a significant risk of misuses of leflunomide for illegal purposes. In addition, leflunomide is available only on prescription, and treatment is to be initiated and supervised by specialists experienced in the treatment of RA and PsA, so the potential for misuse for illegal purposes is considered to be unlikely.

Part II: Module SVII - Identified and potential risks

Safety concerns are harmonised with the EU RMP for the reference product Arava last updated on EMA websites on 03/03/2023.

Part II: 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 fetal toxicity • Progressive multifocal leukoencephalopathy (PML)
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities (such as adverse reactions reporting and signal detection) are considered sufficient for the product.

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)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Hepatic reactions	Routine risk communication: • SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8 • PL sections 2 and 4 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 Zentiva 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: • SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8 • PL sections 2 and 4 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 Zentiva 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: • SmPC sections 4.3, 4.4 and 4.8 • PL sections 2 and 4 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: • SmPC sections 4.3 and 4.6 • PL section 2 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: • SmPC sections 4.4 and 4.8 • PL sections 2 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 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 (PML)	Routine risk communication: • SmPC section 4.4 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

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 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 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 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 ate 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

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatic reactions	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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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. <u>Additional risk minimisation measures:</u> Educational tool for physicians	None
Infections	<u>Routine risk minimisation measures:</u> • 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. <u>Additional risk minimisation measures:</u> Educational tool for physicians	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None
Teratogenicity	<u>Routine risk minimisation measures:</u> • 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.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • Educational tool for physicians • Ad hoc information service for the testing of plasma leflunomide levels	
Male-mediated fetal 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 and 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
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 Zentiva (Leflunomide)
This is a summary of the risk management plan (RMP) for Leflunomide Zentiva. The RMP details important risks of Leflunomide Zentiva and how more information will be obtained about Leflunomide Zentiva's risks and uncertainties (missing information).
Leflunomide Zentiva's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Leflunomide Zentiva should be used.

This summary of the RMP for Leflunomide Zentiva 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 Zentiva's RMP.

I. The medicine and what it is used for

Leflunomide Zentiva is indicated for the treatment of adult patients with:
- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
- active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching (see SmPC for the full indication). Leflunomide Zentiva contains leflunomide as the active substance and it is given by oral route.

Further information about the evaluation of Leflunomide Zentiva's benefits can be found in Leflunomide Zentiva'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-zentiva

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

Important risks of Leflunomide Zentiva, together with measures to minimise such risks and the proposed studies for learning more about Leflunomide Zentiva'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 addition to these measures, information about adverse reactions 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 Zentiva 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 Zentiva. 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).

List of important risks and missing information	
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

The safety information in the proposed Product Information is aligned to the reference medicinal product.

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 Zentiva.

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

There are no studies required for Leflunomide Zentiva.

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 comprises 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

<u>Educational tools for Physician:</u>

- Physician Leaflet
  - Relevant information ofthe safety concem(s) addressed by the aRMM
    The most important risks you should be aware of when prescribing Leflunomide Zentiva® 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 maybe 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 Zentiva is essential.
      - More information about the occurrence of these adverse effects is available in the Summary of Product Characteristics.

      Concomitant administration of Leflunomide Zentiva nd hepatotoxic or hematotoxic DMARDs (e.g., methotrexate) is not advisable.

  - Key message to convey in patients counselling
    - Before starting the treatment with Leflunomide Zentiva, 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 Zentiva 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 Zentiva 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 Zentiva and the necessity to use reliable contraception. Please also discuss the measures to follow in case of inadvertent pregnancy during treatment and after treatments discontinuation. This information should be given before treatment, regularly during treatment and after treatment.
  - Risk on birth defects. Therefore Leflunomide Zentiva 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 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/I 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 Zentiva 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/I 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 Zentiva.
- Wash-out procedure: Plasma levels of the active metabolite of leflunomide, A771726 can be expected to be above 0.02 mg/1 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 Zentiva.

- The wash-out procedure is recommended to accelerate A 771726 elimination, when its needs to be cleared rapidly from the body.

Educational tool for Patient :

• Patient Information Sheet

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

  - Precautions of use for Leflunomide Zentiva

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

After discontinuing Leflunomide Zentiva, 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 Zentiva 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 Zentiva should be guaranteed.
When you want to father a child, you should discuss with your doctor who could advise you stop Leflunomide Zentiva and then undergo the drug wash-out procedure (as described above).
When it is confirmed that Leflunomide Zentiva 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.