Part VI Summary of the risk management plan

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Hepatic reactions • Blood cytopenia • Severe skin reactions, including DRESS • Immunosuppressive effects/Infections • Interstitial lung disease • Teratogenicity • Hypertension
Important potential risks	• Male-mediated fetal toxicity • Lymphoproliferative disorders • Progressive multifocal leukoencephalopathy (PML) • Renal failure • Peripheral neuropathy
Missing information	• Pregnancy and lactation

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

No study planned.

VI.1.4 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Hepatic reactions	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects	NA
Blood cytopenia	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects	NA

Severe skin reactions, including DRESS	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects	NA
Immunosuppressive effects/Infections	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects	NA
Interstitial lung disease	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects	NA
Teratogenicity	Prescription only medicine. Information service for physicians. Included in SPC section(s) • 4.6 Fertility, pregnancy and lactation	Communication and educational program had been performed.
Hypertension	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects	NA
Important potential risks		
Male-mediated fetal toxicity	Included in SPC section(s) • 4.4 Special warnings and precautions for use • 4.6 Fertility, pregnancy and lactation	NA
Lymphoproliferative disorders	Included in SPC section(s) • 4.8 Undesirable effects	NA
Progressive multifocal leukoencephalopathy (PML)	Included in SPC section(s) • 4.4 Special warnings and precautions for use	NA
Renal failure	Included in SPC section(s) • 4.8 Undesirable effects	NA
Peripheral neuropathy	Included in SPC section(s) • 4.4 Special warnings and precautions for use	NA
Missing information		

Pregnancy and lactation	Included in SPC section(s) • 4.3 Contraindications • 4.6 Fertility, pregnancy and lactation	NA

Leflunomide was first approved in 1998. A well-established safety profile based on more than 15 years of post-authorisation experience with the originator product and other generic products exists.

STADA Arzneimittel AG has an adequate Pharmacovigilance System in place.

All potential and identified risks as well as interactions and missing information are sufficiently covered in the respective sections of the SPC. Therefore, no additional pharmacovigilance and risk minimisation activities are deemed necessary.

VI.2 Elements for a Public Summary

<product name> 10 mg film-coated tablets

<product name> 20 mg film-coated tablets

<product name> 100 mg film-coated tablets

VI.2.1 Overview of disease epidemiology

Rheumatoid arthritis (RA) is an autoimmune disease that leads to chronic inflammation of flexible joints, but can also affect other tissues and organs. The prevalence of RA is about 1.0% in industrialised countries. It increases with age and reaches 2.0% in men and women above 55 years. The incidence in Germany lies at 35 to 65 new cases per 100 000 inhabitants. First RA manifestations frequently occur between 35 and 45 years. Women are at a three-fold higher risk than men before the age of 60; after that age, the difference between genders disappears. Symptoms of RA include inflammation of joints, swelling, difficulty moving and pain. Other symptoms that affect the entire body include loss of appetite, fever, loss of energy and anaemia (lack of red blood cells).
Mortality is 2 to 3 fold higher in RA sufferers when compared with the unaffected population. One third of deaths can be directly connected to RA (vasculitis, amyloidosis, atlantoaxial subluxation).

Psoriatic arthritis affects about 10 to 30% of patients suffering from psoriasis, an immune-mediated skin disorder. Psoriatic arthritis can develop at any age, but first occurs between 30 and 55 years of age in the majority of patients . Men and women are equally affected. In about one in seven cases, arthritis symptoms occur before any skin involvement. Symptoms of active psoriatic arthritis include inflammation of joints, swelling, difficulty moving, pain and patches of red, scaly skin (skin lesions).

VI.2.2 Summary of treatment benefits

<product name> belongs to a group of medicines called anti-rheumatic medicines. It contains the active substance leflunomide. The efficacy of leflunomide in the treatment of rheumatoid arthritis was demonstrated in four controlled trials.

<product name> is used to treat adult patients with active rheumatoid arthritis or with active psoriatic arthritis. The efficacy of leflunomide was demonstrated in one controlled, randomised, double blind study. Patients with psoriatic arthritis were treated at 20 mg/day. Treatment duration was 6 months. Leflunomide 20 mg/day was significantly superior to placebo in reducing the symptoms of arthritis in patients with psoriatic arthritis.

VI.2.3 Unknowns relating to treatment benefits

Leflunomide was embryotoxic and teratogenic in rats and rabbits at doses in the human therapeutic range and exerted adverse effects on male reproductive organs in repeated dose toxicity studies. The active metabolite of leflunomide is suspected to cause serious birth defects when administered during pregnancy. Human data are limited.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Liver reactions (Hepatic reactions)	Increase in some liver test results may affect up to 1 in 10 people. Increase in some liver results which may develop into serious conditions such as hepatitis and jaundice may affect up to 1 in 1,000 people. Severe liver injury such as liver failure or necrosis which may be fatal may affect up to 1 in 10,000 people.	Your doctor will carry out **blood tests** at regular intervals, before and during treatment with <product name>, to monitor your liver. It is not recommended to drink alcohol during treatment with <product name>. Drinking alcohol while taking <product name> may increase the chance of liver damage. Tell your doctor **immediately** if you experience: • **tiredness**, **abdominal pain**, or **jaundice** (yellow discolouration of the eyes or skin), as these may indicate serious conditions such as liver failure, which may be fatal.
Imbalance in blood cells (Blood cytopenia)	A slight decrease in the number of white blood cells (leucopenia) may affect up to 1 in 10 people. Other imbalances such as anaemia (decreased number of red blood cells) and thrombocytopenia (decreased number of platelets) may affect up to 1 in 100 people. A marked decrease of some white blood cells (agranulocytosis) may affect up to 1 in 10,000 people.	Your doctor will carry out **blood tests** at regular intervals, before and during treatment with <product name>, to monitor your blood cell counts. Tell your doctor **immediately** if you experience: • **pale skin**, **tiredness,** or **bruising,** as these may indicate blood disorders caused by an imbalance in the different types of blood cells which make up blood.
Severe skin reactions (including DRESS syndrome)	Severe, sometimes life-threatening reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema	Tell your doctor **immediately** and stop taking <product name> if you develop a **skin rash** or **ulcers in your mouth**, as these may

	multiforme, DRESS syndrome) may affect up to 1 in 10,000 people. DRESS syndrome manifests initially as flu-like symptoms and a rash on the face then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cells (eosinophilia) and enlarged lymph nodes.	indicate severe, sometimes life-threatening reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, DRESS syndrome).
(Immunosuppressive effects/Infections)	Severe infections called sepsis, which may be fatal, may affect up to 1 in 1,000 people.	Tell your doctor **immediately** if you experience any symptoms of an **infection** such as **fever, sore throat** or **cough,** as <product name> may increase the chance of a severe infection which may be life-threatening
Inflammation of the lung (Interstitial lung disease)	Inflammation of the lung may affect up to 1 in 1,000 people.	Tell your doctor **immediately** if you experience a **cough** or **breathing problems** as these may indicate inflammation of the lung (interstitial lung disease)
Potential to cause malformations in the fetus (Teratogenicity)	The risk of having a baby with serious birth defects is increased, if you are pregnant or become pregnant while taking <product name>. As it cannot be excluded that <product name> passes into semen, reliable contraception should be used during treatment with <product name> also for men treated with <product name>.	Reliable contraception should be used during treatment of both female and male patients.
High blood pressure (Hypertension)	Mild increase in blood pressure may affect up to 1 in 10 people. Severe increase in blood pressure may affect up to 1 in 1,000 people.	Your doctor will check your blood pressure regularly as <product name> can cause an increase in blood pressure.

Important potential risks

Risk	**What is known** **(Including reason why it is considered a potential risk)**
Male-mediated fetal toxicity	As it cannot be excluded that <product name> passes into semen, reliable contraception should be used during treatment with <product name>. Men wishing to father a child should contact their doctor who may advise them to stop taking <product name> and take certain medicines to remove <product name> rapidly and sufficiently from their body. You will then need a blood test to make sure that <product name> has been sufficiently removed from your body, and you should then wait for at least another 3 months before attempting to father a child.
Lymphoproliferative disorders	The risk of malignancy, particularly lymphoproliferative disorders (elevated numbers of lymphocytes, a type of white blood cell associated with the immune system), is increased with use of some immunosuppressive agents. A clear causal relationship to leflunomide cannot be drawn.
Progressive multifocal leukoencephalopathy (PML)	Rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving leflunomide among other immunosuppressants. A clear causal relationship to leflunomide alone cannot be drawn.
Renal failure	Kidney failure may occur at an unknown frequency.
Peripheral neuropathy	Tell your doctor **immediately** if you experience unusual tingling, weakness or pain in your hands or feet as these may indicate problems with your nerves (peripheral neuropathy).

Missing information

Risk	**What is known**
Pregnancy and lactation	The risk of having a baby with serious birth defects is increased, if you are pregnant or become pregnant while taking <product name>. Tell your doctor if you plan to become pregnant after stopping treatment with <product name>, as you need to ensure that all traces of <product name> have left your body before trying to become pregnant. This may take up to 2 years. **Do not** take <product name> if you are, or think you may be **pregnant**.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation studies have been imposed or are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable