Summary of the Risk Management Plan (RMP) for ARAVA®

ARAVA® (leflunomide)
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of ARAVA® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of ARAVA® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of ARAVA®.

1. THE MEDICINE AND WHAT IT IS USED FOR

ARAVA is authorized 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 (eg, Methotrexate [MTX]) 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). It contains leflunomide as the active substance and it is given by oral route

Further information about the evaluation of ARAVA’s benefits can be found in ARAVA’s EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine’s webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/arava

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of ARAVA together with measures to minimize such risks and the proposed studies for learning more about ARAVA’s risks, are outlined in the next sections

Measures to minimize 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 HCPs;
- Important advice on the medicine’s packaging;
- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of ARAVA these measures are supplemented with additional risk minimization measures (aRMMs) mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

2.1. List of important risks and missing information

Important risks of ARAVA are risks that need special risk management activities to further investigate or minimize 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 ARAVA. 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 (eg, on the long-term use of the medicine);

Table 1 – List of important risks and missing information

Important identified risk	Hepatic reactions Blood cytopenia Infections Teratogenicity
Important potential risk	Male-mediated fetal toxicity Progressive multifocal leukoencephalopathy (PML)
Missing information	None

PML: Progressive Multifocal Leukoencephalopathy.

2.2. **Summary of important risks**

Table 2 – Important identified risk with corresponding risk minimization activities: Hepatic reactions

Hepatic reactions	
Evidence for linking the risk to the medicine	Non-clinical data, clinical data, postmarketing experience
Risk factors and risk groups	• Patients with existing impaired liver function • Co-administration of other hepatotoxic medicinal products • Prior exposure or recent treatment with hepatotoxic medicinal products (eg, MTX)
Risk minimization measures	Routine risk minimization 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 minimization measures: Educational tool for physicians.

PL: Package Leaflet; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 3 – Important identified risk with corresponding risk minimization activities: Blood cytopenia

Blood cytopenia	
Evidence for linking the risk to the medicine	Non-clinical data, clinical data, postmarketing experience.
Risk factors and risk groups	• Patients with pre-existing anemia, leucopenia and/or thrombocytopenia • Patients with impaired bone marrow function or at risk of bone marrow suppression • Prior exposure or recent treatment with hematotoxic medicinal products (eg, MTX)
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.1, 4.2, 4.3, 4.4 and 4.8 • PL Sections 2 and 4 • Recommendations for 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 minimization measures: Educational tool for physicians.

PL: Package Leaflet; PsA: Psoriatic Arthritis; MTX: Methotrexate; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 4 – Important identified risk with corresponding risk minimization activities: Infections

Infections	
Evidence for linking the risk to the medicine	Non-clinical data, clinical data, postmarketing experience.
Risk factors and risk groups	• Elderly patients • Patients immunocompromised predisposing them to reactivation of underlying latent infection
Risk minimization measures	Routine risk minimization 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 • 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 minimization measures: Educational tool for physicians.

PL: Package Leaflet; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 5 – Important identified risk with corresponding risk minimization activities: Teratogenicity

Teratogenicity	
Evidence for linking the risk to the medicine	Non-clinical data, clinical data, postmarketing experience.
Risk factors and risk groups	No particular risk groups or risk factors have been identified.
Risk minimization measures	Routine risk minimization 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 4.4 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 minimization measures: • Educational tools for physicians and patients • Ad hoc information service for the testing of plasma leflunomide levels.

PL: Package Leaflet; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 6 – Important identified risk with corresponding risk minimization activities: Male-mediated fetal toxicity

Male-mediated fetal toxicity	
Evidence for linking the risk to the medicine	Non-clinical data.
Risk factors and risk groups	Not know
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Section 2 • Recommendations for 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 minimization measures: • Educational tools for physicians and patients • Ad hoc information service for the testing of plasma leflunomide levels.

PL: Package Leaflet; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics.

Table 7 – Important identified risk with corresponding risk minimization activities: Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Published case report, postmarketing experience.
Risk factors and risk groups	Recent or concurrent treatment with immunosuppressive agents such as rituximab, infliximab, azathioprine and underlying SLE. The risk could be higher in immunocompromised patients.
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 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 minimization measures: None

PL: Package Leaflet; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SmPC: Summary of Product Characteristics; SLE: Systemic Lupus Erythematosus.

2.3. **Post-authorization development plan**

2.3.1. ***Studies which are conditions of the marketing authorization***

There are no studies which are conditions of the marketing authorization or specific obligation of ARAVA.

2.3.2. ***Other studies in post-authorization development plan***

There are no studies required for ARAVA.