EU-RISK MANAGEMENT PLAN FOR ARAVA® (LEFLUNOMIDE)

Risk Management Plan (RMP) Version number	Version 6.1
Data Lock Point (DLP)	10-SEP-2024
Date of final sign-off	01-DEC-2025

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk Management Plan version 6.1 is prepared to address Type II variation report comments, dated 30-Oct-2025, on RMP version 6.0 (submitted within procedure No. EMA/VR/0000264105). Risk Management Plan version 6.0 has been updated in response to the query raised on the effectiveness and usefulness of the additional risk minimization measures (aRMMs) specifically related to the safety concerns hepatic reactions, blood cytopenia, and infections in periodic safety update report (PSUR) assessment report dated 16-May-2024 under procedure no. EMEA/H/C/PSUSA/00001837/202309.
Summary of significant changes in this RMP	The RMP version 6.0 (Part I, Part II Module SV, Part II Module SVII and Part II Module SVIII, Part V and Part VI) have been updated with new information available at the considered DLP. **Safety concerns:** In the context of Good Pharmacovigilance Practices (GVP) Module V revision 2, the list of safety concerns is updated and the following safety concerns are removed in European Union (EU)-RMP v6.0: Important identified risks of “Hepatic reactions”, “Blood cytopenia”, and “Infections”, **Risk minimization measures:** Update of Part V and Part VI in line with the revised list of safety concerns and aRMMs. **Annexes:** Annex 6 updated for removal of key safety message in the aRMM “Physician leaflet” for the Important identified risks of “Hepatic reactions”, “Blood cytopenia”, and “Infections”. As per Type II variation report comments on EU-RMP v6.0, the key safety message for the aRMM “Physician leaflet” has been updated.

aRMM: Additional Risk Minimization Measure; DLP: Data Lock Point; EMA/EMEA: European Medicines Agency; EU: European Union; GVP: Good Pharmacovigilance Practices; PSUR: Periodic Safety Update Report; PSUSA: Periodic Safety Update Report Single Assessment; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	5.1
Approved with procedure	Procedure number: EMEA/H/C/000235/IB/0081
Date of approval (opinion date)	31-Aug-2022

EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted][a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ACR:	American College of Rheumatology
ADR:	Adverse Drug Reaction
ALT:	Alanine Aminotransferase
aRMM:	Additional Risk Minimization Measure
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under the Curve
bDMARD:	Biological Disease-Modifying Antirheumatic Drug
BMI:	Body Mass Index
CAPD:	Continuous Peritoneal Dialysis
CFTR:	Cystic Fibrosis Transmembrane Conductance Regulator
CI:	Confidence Interval
COPD:	Chronic Obstructive Pulmonary Disease
csDMARD:	Conventional Synthetic Disease-Modifying Antirheumatic Drug
CV:	Cardiovascular
CVD:	Cardiovascular Disease
DDD:	Defined Daily Dose
DLP:	Data Lock Point
DMARD:	Disease-Modifying Anti-Rheumatic Drug
DNA:	Deoxyribonucleic Acid
e-CTD:	Electronic-Common Technical Document
EEA:	European Economic Area
EMA/EMEA:	European Medicines Agency
EPAR:	European Public Assessment Report
EQ-5D:	EuroQoL-5 Dimension
EU:	European Union
EULAR:	European League Against Rheumatism
GVP:	Good Pharmacovigilance Practices
HADS:	Hospital Anxiety and Depression Scale
HCP:	Healthcare Professional
HLA:	Histocompatibility Complex Allele
IBD:	Inflammatory Bowel Disease
IC_{50}:	Half Maximal Inhibitory Concentration
IL:	Interleukin
INN:	International Nonproprietary Name
IRAK1:	Interleukin-1 Receptor-Associated Kinase
ITT:	Intent-to-Treat
JC:	John Cunningham
JRA:	Juvenile Rheumatoid Arthritis
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MBL:	Mannose Binding Lectin
MedDRA:	Medical Dictionary for Regulatory Activities
MTX:	Methotrexate

NOEL:	No Observed Effect Level
NSAID:	Non-Steroidal Anti-Inflammatory Drug
OTIS:	Organization of Teratology Information Specialist
P:	Probability
PBRER:	Periodic Benefit Risk Evaluation Report
PHQ:	Patient Health Questionnaire
PL:	Package Leaflet
PML:	Progressive Multifocal Leukoencephalopathy
PRAC:	Pharmacovigilance Risk Assessment Committee
PsA:	Psoriatic Arthritis
PSUR:	Periodic Safety Update Report
PSUSA:	Periodic Safety Update Report Single Assessment
PT:	Preferred Term
QPPV:	Qualified Person Responsible for Pharmacovigilance
RA:	Rheumatoid Arthritis
RMM:	Risk Minimization Measure
RMP:	Risk Management Plan
RR:	Rate Ratio
RSI:	Reference Safety Information
SD:	Standard Deviation
sDMARD:	Synthetic Disease-Modifying Antirheumatic Drug
SLE:	Systemic Lupus Erythematosus
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
SMR:	Standardized Mortality Ratio
TFMA:	4-Trifluoromethyl Aniline
TNF:	Tumor Necrosis Factor
tsDMARD:	Targeted Synthetic Disease-Modifying Antirheumatic Drug
UK:	United Kingdom
US:	United States
WHO:	World Health Organization

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Leflunomide
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Selective immunosuppressants (L04AK01)
Marketing Authorization Applicant	Sanofi-Aventis Deutschland GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Arava
Marketing authorization procedure	Centralized procedure
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 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, deoxyribonucleic acid (DNA) synthesis and expression of certain cell surface and nuclear antigens directly involved in T-cell activation and proliferation. It inhibits mitogen-stimulated proliferation of human peripheral blood mononuclear cells, and proliferation in transformed murine and human cell lines, in a dose-dependent fashion.
	Important information about its composition Not applicable
Hyperlink to the product information	Refer to electronic-Common Technical Document (e-CTD) sequence 0126, Module 1.3.1 English Product Information.
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 (eg, 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: None
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.*
	Proposed: None
Pharmaceutical form(s) and strength(s)	Current: *Film-coated tablets for oral use.* *Tablet strengths: 10 mg, 20 mg and 100 mg leflunomide.*
	Proposed: None
Is or will the product (be) subject to additional monitoring in the EU?	No

ATC: Anatomical Therapeutic Chemical; DMARD: Disease-Modifying Anti-Rheumatic Drug; DNA: Deoxyribonucleic Acid; EEA: European Economic Area; EU: European Union; e-CTD: Electronic-Common Technical Document; INN: International Nonproprietary Name; RMP: Risk Management Plan.

PART II: SAFETY SPECIFICATION

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

Leflunomide is mainly 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 (eg, 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.

The epidemiology of the disease is summarized in the Table 6 and Table 7.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting the synovium, leading to joint damage and bone destruction and causing severe disability and increased mortality. Several prevalence and incidence studies during the past decades have suggested considerable variations in disease occurrence in different geographical regions, among different populations and over time. [1,2]

Table 6 - Epidemiology of Rheumatoid Arthritis

Indication	Rheumatoid Arthritis
Incidence	The majority of studies carried out in Northern Europe and North America estimate that the annual incidence of RA varies between about 20 and 50 cases per 100 000 inhabitants. [2] Former smokers (Rate ratio [RR] 1.22, 95% confidence interval [CI] 1.10 to 1.36) and current smokers (RR 1.47, 95% CI 1.29 to 1.68) had higher risks of RA. Overweight and obese individuals had 1.27-fold (95% CI 1.09 to 1.48) increased risk of RA. Excess body mass index (BMI) was found to account for 14.73% (95% CI 5.45% to 23.50%) of RA incidence. Low alcohol consumption (Each per 50 g/week increment of alcohol consumption was associated with 8% [95% CI 0% to 16%] reduction in the risk of RA. The fraction of RA risk attributed by low alcohol intake was 8.21% [95% CI 0.31% to 16.39%]).[3] Patients with RA are at high risk of incident overall and fragility fractures. Patients with RA had a higher risk of overall (RR 1.52, 95% CI 1.07-2.14) and fragility (RR 1.61, 95% CI 1.44-1.79) fractures. Subgroup analyses suggested a higher risk of fragility fractures among female patients (31.03 versus 23.75 per 1000 person-years). [4] Patients with RA are at an increased risk of lung and lymphoma malignancies compared with the general population. [5] Rheumatoid Arthritis patients were reported to present an excess risk of fatal myocardial infarction compared to the general population. [6] Patients with RA appear to be at higher risk of lymphoma and lung

<table>
<tr><th>Indication</th><th>Rheumatoid Arthritis</th></tr>
<tr><td></td><td>cancer. [7] A review from Alamanos, 2006 detailed the worldwide incidence of RA in studies, based on the 1987 American College of Rheumatology (ACR) Criteria:
<table>
<tr><th>Country (Year of the publication)</th><th>Incidence cases/1000 inhabitants</th><th>Population Age</th></tr>
<tr><td>US (2002)</td><td>0.5</td><td>≥18</td></tr>
<tr><td>US (2010)[a]</td><td>0.409 (2007 data)</td><td>≥18</td></tr>
<tr><td>France (1994)</td><td>0.1</td><td>20-70</td></tr>
<tr><td>Finland (2003)</td><td>0.4</td><td>≥16</td></tr>
<tr><td>Greece (1997)</td><td>0.2</td><td>≥15</td></tr>
<tr><td>Norway (2000)</td><td>0.3</td><td>≥20</td></tr>
<tr><td>Spain (2008) [8]</td><td>0.1</td><td>≥16</td></tr>
<tr><td>Sweden (2010) [9]</td><td>0.5</td><td>≥20</td></tr>
<tr><td>UK (2005)</td><td>0.2</td><td>≥15</td></tr>
<tr><td>Japan (1999)</td><td>0.1</td><td>All ages</td></tr>
</table>
a Latest data 2007, Olmsted County Minnesota [10]
UK: United Kingdom; US: United States.</td></tr>
<tr><td>Prevalence</td><td>The majority of studies carried out in Northern Europe and North America estimate that the prevalence of RA is from 0.3% to 1.1%. [2]
<table>
<tr><th>Country (Year of the publication)</th><th>Incidence cases/1000 inhabitants</th><th>Population Age</th></tr>
<tr><td>US (1999)</td><td>10.7</td><td>≥35</td></tr>
<tr><td>US (2010)[a]</td><td>7.2 (2005 data)</td><td>≥18</td></tr>
<tr><td>England (2002)</td><td>8.5</td><td>≥16</td></tr>
<tr><td>Finland (2001)</td><td>18</td><td>65-85</td></tr>
<tr><td>France (2005)</td><td>3.1</td><td>≥18</td></tr>
<tr><td>Greece (2003)</td><td>7.0</td><td>All ages</td></tr>
<tr><td>Italy (1998)</td><td>3.3</td><td>≥16</td></tr>
<tr><td>Norway (2000)</td><td>4.7</td><td>≥20</td></tr>
<tr><td>Spain (2002)</td><td>5.0</td><td>≥20</td></tr>
<tr><td>Japan (1999)</td><td>1.7</td><td>All ages</td></tr>
<tr><td>Sweden (2010) [9]</td><td>6.6</td><td>≥20</td></tr>
<tr><td>China (2003)</td><td>2.8</td><td>≥16</td></tr>
<tr><td>Argentina (2002)</td><td>2.0</td><td>≥16</td></tr>
</table>
a latest data 2005, Olmsted County Minnesota [10]
US: United States.
A review from Alamanos, 2006 [2] detailed the worldwide prevalence of RA (ACR).</td></tr>
</table>

Indication	Rheumatoid Arthritis
	Global: The global RA prevalence (95% CI) was 0.46 (0.39-0.54) [4] The RA point-prevalence was: [11] • 0.45% (95% CI 0.38-0.53%) between 1986 and 2014; • 0.46% (95% CI 0.36% and 0.57%) from 1955 to 2015. **South America:** Pooled prevalence of RA resulted in 0.48% with 591 981 cases in a population of 114 537 812 individuals. [12] • Subgroup range: From Venezuela 0.86% (0.41-1.77) to Colombia, 0.24% (0.15-0.39) and Brazil 0.22% (0.05-0.91); • Indigenous population 1.45% (higher). Point prevalence reported (0.00-2.70%) and mean of 0.56% (Standard deviation [SD] 0.51) between 1986 and 2014, and Mean period prevalence of 0.51% (SD 0.35) between 1955 and 2015. Rheumatoid Arthritis point and period prevalence was higher in urban settings (0.69% versus 0.48%) than in rural settings (0.54% versus 0.25%). [13] • Age: Risk factors for RA related bronchiectasis were older age; [14] • Longer RA duration; [14] • Genetics (Cystic fibrosis transmembrane conductance regulator (CFTR) and Histocompatibility Complex Allele [HLA]); [14] • Undetectable circulating Mannose Binding Lectin (MBL) as a biomarker. [14] • Age: The main influence on depression prevalence was the mean age of the sample. [15] • Prevalence of RA according to different categories: [11] Pooled prevalence by geographic population: • Urban populations, 0.48% (95% CI 0.42-0.57) (the highest pooled prevalence) (rural populations 0.36% [95% CI 0.21-0.53]), • Over time in urban population: Rheumatoid Arthritis pooled prevalence among urban populations in 2001-2018, 0.70% (95% CI 0.63-0.77) was significantly higher than 1986-2000 and 0.39% (95% CI 0.28-0.50). • Income (at country level): The pooled prevalence was higher in high-income countries (0.49% [95% CI 0.39-0.59]), upper-middle-income countries (0.47% [95% CI 0.34-0.62]) and lower-middle income countries (0.35% [95% CI 0.20-0.53]). • Indigenous population: Prevalence was higher among the indigenous population in South America; 1.45%. [12]
Demographics of the population in the authorized indication	Both prevalence and incidence rates are reportedly about 2 to 4-fold higher in women than in men, and symptoms appear to be more severe in women. RA may present at any age; however, patients are most commonly first affected in the third to sixth decade of life. The prevalence peaked at age 70-79 years (women = 2.1%, men = 1.1%) before dropping in those aged 80 years. [9] Female gender and genetic factors are the main risk factor for RA. Pooled EuroQoL-5 Dimension (EQ-5D) utility scores of RA were associated with severe disease activity, increasing age and female gender among RA patients. [16] Higher risk of fragility fractures among female patients (31.03 versus 23.75 per 1000 person-years). [4] Female has higher risk factor for cervical spine involvement in RA were female gender. [17]

Indication	Rheumatoid Arthritis
	Genetic susceptibility and ethnicity: The existence of major HLA encoded susceptibility was detected in population studies and family studies. The class II major histocompatibility complex allele HLA-DR4 (DR β 1*0401) and related alleles are known to be major genetic risk factors for RA It has been estimated that the risk of developing RA in a person with DR β 1*0401 or the closely related DR β 1*0404 is 1 in 35 and 1 in 20 respectively, whereas the presence of both alleles puts persons at an even greater risk. [18] Interleukin-6-174G/C gene polymorphism were associated with increased risk of RA in Asians, but not in Caucasians. [19] **Ethnicity**: Interleukin-17 Gene Polymorphism (s2275913 G allele) increases the risk of RA in Caucasians, but not in Mongolians. [20] Genetic variant in miR-146a gene. [21] The structural polymorphisms in exon 1 of mannose-binding lectin gene was associated with RA in Brazilian and Indian populations, the functional polymorphisms in the promoter region was associated with RA in East Asians. [22] Three polymorphisms of Interleukin-1 Receptor-Associated Kinase (IRAK1) gene, rs3027898, rs1059702 and rs1059703, were related to RA risk. [23] Asp299Gly and Thr399Ile have a protective effect on Spanish populations, the 2 polymorphisms could act as a susceptible factor in Chinese Han populations. [24] ITGAV gene rs3768777 polymorphisms among Caucasians. [25] C allele in PTPN22-1123 increased the risk of RA only in Non-Asians. [26] **Gender susceptibility:** Sex is the major genetic factor, as RA predominantly affects females. However, sex could influence mainly the penetrance of the disease (the proportion of genetically susceptible individuals developing the disease). There is no genetic epidemiology evidence for the presence of RA genes on the X-chromosome. [27] The overall occurrence of RA is two to four times greater in women than men. [28,] **Other factors:** Genetic risk factors and sex do not fully account for the incidence of RA, suggesting that environmental factors also play a role in the etiology of the disease. This is emphasized by epidemiologic studies in Africa that have indicated that climate and urbanization have a major impact on the incidence and severity of RA in groups of similar genetic background. Smoking has clearly been identified as a risk for RA in persons expressing an HLA-β 1 susceptibility allele. [18]
Main existing treatment options	Medications that are used to treat RA are divided into three main classes: Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and DMARDs, [29] but the management of RA rests primarily on the use of DMARDs. [30] Disease-Modifying Antirheumatic Drugs form two major classes: Synthetic disease-modifying antirheumatic drugs (sDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs). A proposal for a new nomenclature was recently published, [31] including the following categories: • **Conventional synthetic DMARDs (csDMARDs)**: Methotrexate (MTX), sulfasalazine, leflunomide, hydroxychloroquine, gold salts • **Targeted synthetic DMARDs (tsDMARDs)**: tofacitinib • **Biological originator DMARDs**: Tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the T cell costimulation inhibitor, abatacept, the anti-B cell agent, rituximab, and the Interleukin (IL)-6 receptor-blocking monoclonal antibody, tocilizumab, as well as the IL-1 inhibitor, anakinra. • **Biosimilars DMARDs**: bs-infliximab. Based on current European League Against Rheumatism (EULAR) recommendations, [30] MTX should be part of the first treatment strategy in patients

Indication	Rheumatoid Arthritis
	with active RA. In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy. In DMARD-naive patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used. If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered. In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors, abatacept or tocilizumab, and, under certain circumstances, rituximab) should be commenced with MTX. If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor or a biological agent with another mode of action. Tofacitinib may be considered after biological treatment has failed.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Rheumatoid arthritis has traditionally been regarded as having an essentially non-fatal outcome; however, studies conducted over the past four decades have found that it is associated with increased mortality in comparison with the general population of the same age and gender. Most studies indicate that the increased mortality is due to cardiac diseases [32] however it has not been demonstrated in all studies. The extent of the increased risk has not been consistent, and standardized mortality ratios have been reported to range from 1.16 to 3.0 in studies conducted in various countries. Recent studies among various populations in North America and the United Kingdom (UK) have reported standardized mortality ratios of 1.32 to 3.05, while studies in Sweden and Norway reported values of 1.57 and 2.0, respectively.
Important co-morbidities	Important co-morbidities found in the target population: Rheumatoid arthritis is often characterized by the burden of swollen joints, pain, and decreased physical function, but less well understood are the many manifestations of additional health conditions that are associated with RA and its treatment. [33] Studies noted the increased rates of cardiovascular (CV) and infection events in patients with RA. The chronic, debilitating, autoimmune nature of RA affects the patient directly or indirectly in almost all organ systems, from CV problems and infections to depression and gastrointestinal ulcers. On average, a patient with established RA has two or more comorbid conditions. The discharge diagnoses of patients with RA, during the period 01-Jan-1997 to 31-Dec-2000, were retrieved from the database of the Department of Internal Medicine of the University of Genova, Italy. [34] The most frequently observed comorbidities were cardiovascular disease (CVD) (34.6%), hypertension (14.5%) and angina (3.5%), followed by gastrointestinal (24.5%), genito-urinary (18.7%) and respiratory (17%) diseases. Respiratory: • Body Mass Index was significantly associated with obstructive sleep apnea (standardized mean difference 1.08; probability (P) = 0.044). [35] • Rheumatoid arthritis-related bronchiectasis is a common extra-articular feature of RA with a pooled overall prevalence of among RA was 18.7% (95% CI 13.7-24.3%). [36] • The overall pooled prevalence of obstructive sleep apnea was 29.8% (95% CI 15.2-46.7; I^2 = 99.6%) in the patients with RA. [35] • Assessment based on the Berlin Questionnaire© for Sleep Apnea resulted in a more precise estimate of OSA prevalence with reduced heterogeneity

Indication	Rheumatoid Arthritis
	(prevalence 45.3%; 95% CI 37.4-53.3; I^2 = 58.8%). Increased risk of subsequent development of chronic obstructive pulmonary disease (COPD). [37] Cardiovascular: • RA cases has a higher prevalence of Asymptomatic coronary artery disease (RR = 1.26 [95% CI 1.04-1.52]; P = 0.021) compared to controls. With higher weighted mean differences for coronary calcium score (48.25 [95% CI 26.97-69.53]; p < 0.001) compared to controls (more multivessel disease, and more high-risk plaques compared to controls). [38] • Increased risk of subsequent development of atrial fibrillation among patients with RA. [39] • Hypertension, type 2 diabetes, smoking, hypercholesterolaemia and obesity increase CVD risk in patients with RA. [40] Depression: The prevalence of major depressive disorder to be 16.8% (95% CI 10%, 24%). [15] • By Patient Health Questionnaire (PHQ)-9, 38.8% (95% CI 34%, 43%), • By Hospital Anxiety and Depression Scale (HADS) with thresholds of 8 and 11 were 34.2% (95% CI 25%, 44%) and 14.8% (95% CI 12%, 18%), respectively. The main influence on depression prevalence was the mean age of the sample. Other: • Metabolic Syndrome: The prevalence of Metabolic syndrome in RA populations was 0.31±0.04 (95% CI 0.27-0.35). [41] • Rheumatoid cachexia: The estimated overall prevalence of rheumatoid cachexia (low muscle mass without weight loss in RA patients) was frequent 19% (95% CI 07%-33%). [42] • Temporomandibular disorders: Typical difficulties experienced by RA patients included impaired swallowing (24.63%), impaired masticatory ability (30.69%), masticatory pain (35.58%), and masticatory fatigue (21.26%). [43] Three co-morbidities of RA are as follows: • Hypertension • Cardiovascular disease • Pulmonary diseases Concomitant medications in the target population: Leflunomide is commonly used with anti-inflammatory drugs (mainly NSAIDs), corticosteroids including oral as well as intra-articular. The combination of leflunomide with other DMARDs is not fully studied. A Sanofi sponsored drug utilization study was conducted in three European countries, and it concluded that leflunomide is commonly used as single agent rather than in combination with MTX. Since such therapy can lead to additive or even synergistic toxicity (eg, hepato- or hematotoxicty) hence, the benefits and risks of combination DMARDs therapy should be weighed individually for each patient. The use of leflunomide with antimalarials used in rheumatic diseases (eg, chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents including TNF alpha-inhibitors has also not been adequately studied up to now in randomized trials. Concomitant use with conventional DMARDs (based on data of MTX) are important identified interactions and are described in [Part II Module SVII]. The patient with RA also frequently suffer from hypertension, CVD, depression, orthopedic problems and pulmonary diseases hence, numerous other concomitant medications can be administered depending upon the other co-morbidities as follows.

Indication	Rheumatoid Arthritis
	• Anti-inflammatory drugs (mainly NSAIDs), • Corticosteroids including oral as well as intra-articular, • Antimalarials used in rheumatic diseases (eg, chloroquine and hydroxychloroquine), • Intramuscular or oral gold, • D-penicillamine, • Azathioprine and other, • Immunosuppressive agents including tumor necrosis factor alpha-inhibitors, • Conventional DMARDs (based on data of MTX) and biological DMARDs.

ACR: American College of Rheumatology; bDMARD: Biological Disease-Modifying Antirheumatic Drug; BMI: Body Mass Index; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; csDMARD: Conventional Synthetic Disease-Modifying Antirheumatic Drug; COPD: Chronic Obstructive Pulmonary Disease; CI: Confidence Interval; CV: Cardiovascular; CVD: Cardiovascular Disease; DMARD: Disease-Modifying Antirheumatic Drug; EQ-5D: EuroQoL-5 Dimension; EULAR: European League Against Rheumatism; HADS: Hospital Anxiety and Depression Scale; HLA: Histocompatibility Complex Allele; IL: Interleukin; IRAK1: Interleukin-1 receptor-Associated Kinase; MTX: Methotrexate; MBL: Mannose Binding Lectin; NSAID: Non-Steroidal Anti-Inflammatory Drug; P: Probability; PHQ: Patient Health Questionnaire; RA: Rheumatoid Arthritis; RR: Rate Ratio; sDMARD: Synthetic Disease-Modifying Antirheumatic Drug; SD: Standard Deviation; tsDMARD: Targeted Synthetic Disease-Modifying Antirheumatic Drug; TNF: Tumor Necrosis Factor; UK: United Kingdom; US: United States.

Psoriatic Arthritis

Psoriatic Arthritis (PsA) is commonly defined as psoriasis associated with chronic, erosive inflammatory arthritis, which is seronegative for rheumatoid factor. Psoriatic Arthritis lies somewhere between rheumatoid polyarthritis and spondyloarthropathy.

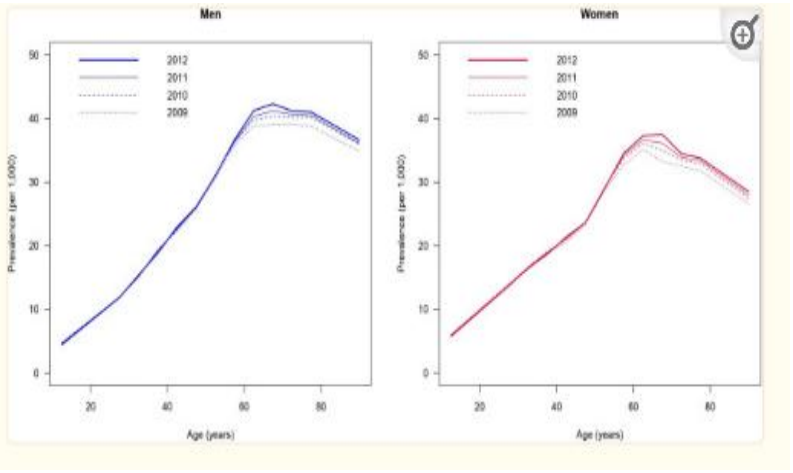
In 10% to 15% of cases, rheumatologic manifestations are observed before skin lesions.

The epidemiologic profile of PsA is likely to present important variations among countries and areas of the world. However, several methodological issues and mainly the absence of validated or consensual criteria for case identification and classification of the disease put important limitations on the interpretation of epidemiological data. [44]

Table 7 - Epidemiology of Psoriatic Arthritis

Indication	Psoriatic Arthritis
Incidence	The reported incidence of PsA varies from 3.4 to 8 per 100 000 inhabitants. [45] In a survey covering a total of 13 studies reported in the literature, [44] there is a wide variation in the annual incidence of PsA with a median of 6.4 cases per 100 000 inhabitants (range 0.1-23.1). Global: The random effect pooled PsA: [46] • Prevalence: 133 every 100 000 subjects (107-164 every 100 000 subjects); • Incidence: 83 every 100 000 Person-years (95% CI, 41-167 every 100 000 Person-years). Germany: Sex-specific incidence of PsA were: [47] • In women (40 per 100 000 Person-years [higher]); • In men (30 per 100 000 Person-years [lower]).

Indication	Psoriatic Arthritis
Prevalence	The exact prevalence of PsA is unknown and estimation is difficult, in part due to the lack of widely accepted classification or diagnostic criteria, however estimates vary from 40 per 100 000 to 1200 per 100 000 of the general population. [48] In a United States (US) study, prevalence was 250 per 100 000. [49] In the survey mentioned above, the prevalence of PsA varied from 1 per 100 000 in a Japanese study, to 420 per 100 000 in an Italian study (median 108). Ever smoking increases the risk of psoriasis in the general population but may reduce the risk of PsA in psoriasis patients. [50] Enthesitis, dactylitis and nail disease are highly prevalent in PsA, but not uveitis and inflammatory bowel disease (IBD). [51] While patients with psoriasis have a slightly increased risk of cancer, PsA does not have it. [52] The pooled proportion (95% CI) of PsA among patients with psoriasis was 19.7% (18.5%-20.9% [1 in 4 patients with psoriasis have PsA]). [53] Ethnicity: Prevalence among patients with psoriasis were: [53] • 22.7% (20.6%-25.0%) in European; • 21.5% (15.4%-28.2%) in South American; • 19.5% (1%-22.1%) in North American patients; • 15.5% (0.009%-51.5%) in African; • 14.0% (11.7%-16.3%) in Asian. Overall, among children and adolescents (<18 years of age), the pooled prevalence was 3.3% (2.1%-4.9%). [53] The prevalence of undiagnosed psoriatic arthritis among psoriasis patients were: [54] • 15.5% when all studies were considered; • 10.1% when only epidemiological studies were considered. Weight loss improves pre-existing psoriasis and PsA and prevent the onset of psoriasis in obese individuals. [55]
Demographics of the population in the authorized/proposed indication	Psoriatic arthritis does not appear to have gender-specific prevalence or incidence, however as with RA. The mean age at diagnosis varied between 40.7 and 52.0 years (median 47.7) [27] and patients are most commonly first affected in the third to sixth decade of life. [45] Like RA, PsA also have mainly genetic predisposition. First-degree relatives of PsA patients have an elevated risk for psoriasis, in monozygotic twins, the concordance for psoriasis is ≥65%, and for PsA ≥30%. A variety of HLA associations have been found. HLA-DR7, HL DQ3, and HLA-B57 are associated with PsA because of linkage disequilibrium with Cw6. Other associations include HLA-B13, HLA-B37, HLA-B38, HLA-B39, and HLA-DR4. The MIC A A9 allele at the HLA-B-linked MIC-A locus has also recently been reported associated with PsA, as have certain killer immunoglobulin-like receptor alleles. [56] **Gender-specific and Age:** Germany: The maximum sex-specific incidence of PsA was higher in women (40 per 100 000 Person-years) than in men (30 per 100 000 Person-years). [47]

Indication	Psoriatic Arthritis
	Figure 7a: Age-specific and sex-specific prevalence of psoriasis (per 1000) in Germany between 2009 and 2012  The age-specific incidence of PsA continuously increase with rising age until it peaked slightly before the age of 60 years and declined thereafter. Genetic Predisposition: Class I chain-related gene A transmembrane (MICA-TM) A9 allele is associated with a psoriatic arthritis risk in Europeans. [57] PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis. [58] Among identified psoriasis risk variants, two were more strongly associated with PsA than Psoriasis vulgaris (rs12044149 near IL23R, P = 0.00018; rs9321623 near TNFAIP3, P = 0.00022). [59] HLA-C gene is associated with PsA in populations of European and Middle Eastern descent. [60] At both the allelic and phenotypic levels: [60] • HLA-C*02, *06 and *12 may contribute to susceptibility to PsA; • HLA-C*04 may confer a protective role against PsA.
Main existing treatment options	Treatment of PsA is challenging due to the heterogeneity of clinical presentation with diverse articular and dermatological features as well as varied disease course and outcomes. Besides NSAIDs and corticosteroids, current options include synthetic DMARDs and anti-TNF therapy. Based on current EULAR recommendations, [61] NSAIDs should be used as first-line treatment for symptomatic relief. In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C-reactive protein and/or clinically relevant extra-articular manifestations), treatment with DMARDs such as MTX, leflunomide, or sulfasalazine should be considered at an early stage (commonly regarded as a few weeks to a maximum of one year). Methotrexate is recommended as the first choice. In patients with active arthritis and an inadequate response to at least one synthetic DMARD, such as MTX, therapy with TNF-I should be commenced.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Information on mortality in PsA is sparse and conflicting: a mortality study from the University of Toronto Psoriatic Arthritis Clinic found patients with PsA to be at increased risk of death compared to the general Ontario population. This study found a combined Standardized Mortality ratio for both men and women of 1.62 (95% CI 1.21, 2.12). [62] A subsequent study in 2007 from the same cohort did however, showed a trend toward improved survival over the past 3 decades: [63] after performing 10 year rolling standardized mortality ratio (SMR) calculations, Ali et al [64] found that the SMR was generally higher in this population earlier on, and the estimated SMR of 1.05 over approximately the last decade was much smaller than

Indication	Psoriatic Arthritis
	those for the previous 2 decades, with SMRs of 1.89 and 1.63, respectively. The study thus demonstrated a trend for improvement in survival in these patients. Moreover, a single center study from the UK did not demonstrate any significant difference in mortality between authors PsA cohort and that of the general UK population. [63] In Canada, increased mortality was reported in large studies involving 428 and 680 patients with PsA. [65] Cardiovascular related disease was the most common cause of death, followed by respiratory diseases, cancer, injuries and poisoning. Deaths from respiratory disease, CVD and injuries and poisoning were found to be higher than those in the general population. Predictors for mortality include a high sedimentation rate and radiological damage at presentation. In a Canadian study involving 648 patients with PsA, 18.8% developed hypertension: 5.9% had myocardial infarction, and 0.8%, 3.2% and 1.7% had cerebral vascular accident, angina and congestive heart failure, respectively. [66] A total of 155 patients (23.9%) had at least one of these conditions. Patients with PsA are therefore at increased risk of CV morbidities and mortality, compared to the general population. The standardized prevalence ratios in these PsA patients were 1.90 for hypertension, 2.57 for myocardial infarction, 1.97 for angina and finally 1.19 for congestive heart failure.
Important co-morbidities	Important co-morbidities found in the target population: Rheumatoid arthritis is often characterized by the burden of swollen joints, pain, and decreased physical function, but less well understood are the many manifestations of additional health conditions that are associated with RA and its treatment. [33] Studies noted the increased rates of CV and infection events in patients with RA. The chronic, debilitating, autoimmune nature of RA affects the patient directly or indirectly in almost all organ systems, from CV problems and infections to depression and gastrointestinal ulcers. On average, a patient with established RA has two or more comorbid conditions. The discharge diagnoses of patients with RA, during the period 01-Jan-1997 to 31-Dec-2000, were retrieved from the database of the Department of Internal Medicine of the University of Genova, Italy. [34] The most frequently observed comorbidities were CVD (34.6%), hypertension (14.5%) and angina (3.5%), followed by gastrointestinal (24.5%), genito-urinary (18.7%) and respiratory (17%) diseases. The most prevalent comorbidities were: [67] • Hypertension (pooled prevalence 34%); • Metabolic syndrome (29%); • Obesity (27%); • Hyperlipidemia (24%); • Any CVD (19%). Incidence of depression and anxiety was significantly higher among cases of PsA. [68] Anxiety and depression are highly prevalent among PsA patients. [69] A moderate point prevalence of depression and anxiety in patients slightly higher than the general population and comparable to that seen in other rheumatic diseases. [70] Three co-morbidities of RA are as follows: • Hypertension • Cardiovascular disease • Pulmonary diseases Concomitant medications in the target population: Leflunomide is commonly used with anti-inflammatory drugs (mainly NSAIDs), corticosteroids including oral as well as intra-articular.

Indication	Psoriatic Arthritis
	The combination of leflunomide with other DMARDs is not fully studied. A Sanofi sponsored drug utilization study was conducted in 3 European countries and it concluded that leflunomide is commonly used as single agent rather than in combination with MTX. Since such therapy can lead to additive or even synergistic toxicity (eg, hepato- or hematotoxicty) hence, the benefits and risks of combination DMARDs therapy should be weighed individually for each patient. The use of leflunomide with antimalarials used in rheumatic diseases (eg, chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive agents including tumor necrosis factor alpha-inhibitors has also not been adequately studied up to now in randomized trials. Concomitant use with conventional DMARDs (based on data of MTX) are important identified interactions and are described in [Part II Module SVII]. The patient with RA also frequently suffer from hypertension, cardiovascular diseases, depression, orthopedic problems and pulmonary diseases hence, numerous other concomitant medications can be administered depending upon the other co-morbidities as follows. • Anti-inflammatory drugs (mainly NSAIDs); • Corticosteroids including oral as well as intra-articular; • Antimalarials used in rheumatic diseases (eg, chloroquine and hydroxychloroquine); • Intramuscular or oral gold; • D-penicillamine; • Azathioprine and other; • Immunosuppressive agents including tumor necrosis factor alpha-Inhibitors; • Conventional DMARDs (based on data of MTX) and biological DMARDs.

CI: Confidence Interval; CV: Cardiovascular; CVD: Cardiovascular Disease; DMARD: Disease Modifying Antirheumatic Drug; EULAR: European League Against Rheumatism; HLA: Histocompatibility Complex Allele; IBD: Inflammatory Bowel Disease; MTX: Methotrexate; NSAID: Non-Steroidal Anti-Inflammatory Drug; P: Probability; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SMR: Standardized Mortality Ratio; TNF: Tumor Necrosis Factor; UK: United Kingdom; US: United States.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The data presented in this section are summarized from the original marketing authorization application, submitted in February 1998, referring to non-clinical studies performed during the development program for leflunomide, which was completed in the late 1990s. No new relevant non-clinical data on leflunomide have been generated since that time.

The toxicological studies performed during the non-clinical development program for leflunomide indicated potential toxicities involving various organ systems. The effects seen in bone marrow, blood, gastrointestinal tract, skin, spleen, lymph nodes and thymus, after both single and repeated administration, and the teratogenicity and embryotoxicity observed in various reproduction studies reflect, directly or secondarily, the basic mechanism of action of leflunomide, which essentially involves impairment of DNA synthesis by inhibition of pyrimidine biosynthesis.

Other toxicity seen in the heart, liver, cornea and respiratory system were considered to be correlated with the immunosuppressive effects of leflunomide, facilitating bacterial and viral infections.

In addition, toxic effects on reproductive organs, characterized by atrophy of ovaries and uterus, as well as degeneration and atrophy of testes, prostate and seminal vesicles were seen and were considered to be due to the pharmacodynamic activity of leflunomide, ie, its cytostatic effects on rapidly developing cells.

The key non-clinical findings are presented in the following table.

Table 8 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • **Key issues identified from acute or repeat-dose toxicity studies** *Hematological studies* Leflunomide was well tolerated in mice up to dose levels of 15 mg/kg. At 30 mg/kg and higher doses, hematological effects, ie, anemia, lower platelet counts and lymphoid atrophy (spleen, lymph nodes, and thymus) were observed. The hematological effects were considered to be correlated with the cytotoxic effects of leflunomide and the hematotoxicity of 4-trifluoromethyl aniline (TFMA), a minor metabolite of leflunomide. The primary toxicity of leflunomide in rats was expressed in hematological effects and changes in the bone marrow, characterized by anemia (decreases in erythrocytes, hemoglobin and hematocrit), leucopenia and decreased platelet counts, and marked depletion of hematopoietic cells in the bone marrow (panmyelopathy). Increased extramedullary splenic erythropoiesis was generally noted, however thrombocytopoiesis was mostly missing in the spleen. Thus, the hemorrhages detected in various organs (gastrointestinal tract, meninges, lymph nodes, thymus and central nervous system can be regarded as being caused by thrombocytopenia. The lowest observed effect level for any hematological changes was 1 mg/kg in the 6 month study,	Two types of hematological effects were observed in preclinical toxicity studies: central effects and peripheral effects due to the active metabolite of leflunomide, A771726. In the majority of preclinical toxicity studies, systemic exposure of animals to A771726 was assessed, since leflunomide is very rapidly transformed to its active metabolite. However, in all toxicity studies, it was impossible to generate safety margins based on systemic exposure to A771726. The lowest NOEL for leflunomide (0.5 mg/kg in the 6 month rat study) yielded an area under the curve (AUC) value of 9.16 µg*h/mL compared to an estimated AUC in humans of 1000 µg*h/mL at steady state and at the expected therapeutic dose of 20 mg/day. There appears to be a plausible mechanistic explanation for why blood concentrations not associated with significant adverse effects in humans can be many times higher than those that demonstrate toxicity in animals. The concentration of A771726 required to produce 50% inhibition of Dihydroorotate dehydrogenase in humans is 41 and 8-fold higher than that required in rats and mice

Key Safety Findings	Relevance to human usage
and the no observed effect level (NOEL) in the study was 0.5 mg/kg/day. A771726 was tested in 2 intravenous studies in rats over 1 month, and similar hematological and bone marrow changes were seen. The NOEL for any hematological changes was 0.25 mg/kg. In dogs, there was evidence of toxic hemolytic anemia and, histologically, bone marrow hyperplasia, extramedullary hematopoiesis and hemosiderosis in spleen, liver and bone marrow were noted. In the 6 month study, the NOEL for hematological changes was 0.8 mg/kg, whereas in the 12 month study, transient effects were still noted at the lowest dose tested (0.25 mg/kg). The pronounced hemolytic anemia in dogs is considered to be correlated with the formation of TFMA and the slower detoxification of this metabolite in dogs due to N-acetylation deficiency in this species.	respectively. Similarly, the ability of A771726 to inhibit cell proliferation is species dependent. The half maximal inhibitory concentration (IC_{50}) for antiproliferative activity in human tissue is 328 and 3-fold higher than that for rats and mice respectively. As a result, it is difficult to extrapolate the findings to human usage, primarily due to species differences with regard to pharmacokinetics and the enzyme-site of action. As a conclusion of non-clinical data, blood cytopenia is considered an important identified risk.
Hepatic effects Increased liver weights and elevated aspartate aminotransferase (AST) values were observed after oral dosing of leflunomide at or above 4 mg/kg in rats. In addition, hepatic necroses were found in animals that died inter-currently and/or were infected with Bacillus piliformis. Similar, but more pronounced liver changes were observed with A771726 at dose levels of 3.2, 8 and 20 mg/kg intravenously. Leflunomide caused liver changes in rats, although it was in some animals difficult to determine if the hepatic necrosis was due to Bacillus piliformis infection or secondary hypoxia after myocardial necrosis or a direct hepatotoxic effect of the drug. Increased liver weights were noted in the 3 month study in dogs dosed at 8 mg/kg. AST was increased in 3 males in the 16 mg/kg group and hepatic necrosis occurred in animals that died inter-currently. No signs of hepatotoxicity were seen in the 6 and 12 month studies. In the 1 month intravenous study, alanine aminotransferase (ALT) (1 male) and alkaline phosphatase (2 females) were slightly increased in the high-dose group.	In pre-clinical toxicity studies, three types of hepatic effects were observed: increased liver weight, increased liver enzyme levels (primarily AST) and necrosis, although it was in some cases difficult to determine whether the latter was related to bacterial infection or to a hepatotoxic effect of leflunomide. As described above for the hematological effects, it is difficult to extrapolate these findings to human usage, primarily due to species differences with regard to pharmacokinetics and the enzyme-site of action. As a conclusion of non-clinical data, hepatic reactions is considered an important identified risk.
• **Reproductive/developmental toxicity studies** *Teratogenicity* In animal reproductive toxicity studies, leflunomide was found to be both embryotoxic and teratogenic in rats and rabbits. The effects were observed at levels at or below those achieved in humans, and rats appeared to be more sensitive to the effects. At 15 mg/kg/day, anophthalmia, microphthalmia and hydrocephalus were observed in rat offspring, as well as abnormalities of rump, vertebrae, ribs and limbs, along with marked decreases in postnatal survival. In rabbits dosed at 10 mg/kg/day, offspring had malformations of the head and bilateral dysplasia of the spine of the scapula. The NOEL for embryotoxicity and teratogenicity in rats and rabbits was 1 mg/kg.	Teratogenic effects were observed in preclinical toxicity studies; however, as described above for hematological effects, it is difficult to extrapolate the findings to human use due to species differences. Congenital anomalies, when reported in the context of human use, are not consistent with those noted in animal developmental toxicity studies (See [Part II Module SIV]). As a conclusion of non-clinical data, teratogenicity is considered an important identified risk.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUC: Area Under the Curve; IC_{50}: Half Maximal Inhibitory Concentration; NOEL: No Observed Effect Level; TFMA: 4-Trifluoromethyl Aniline.

Safety findings in special populations

There are no special populations requiring specific non-clinical data.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The clinical development program of leflunomide in the indication of RA consisted in 11 clinical studies, summarized as follows:

- Six uncontrolled, Phase-II studies:
  - Studies B1 and B2: 6 week, open-label, dose-ranging studies
  - Study B4: 6 month, double-blind, randomized study to elucidate pharmacokinetics
  - Study B5: open-label extension of Studies B3 and B4
  - Study B6: 6 month, single-blind, randomized study to compare two weekly dosages of leflunomide (as opposed to daily doses in the other studies)
  - Study B7: open-label extension of Study B6 with weekly doses
- One double-blind, randomized, placebo-controlled, Phase-II study:
  - Study B3: 6 month dose-finding study
- Four double-blind, randomized, controlled, Phase-III studies:
  - Study B8: 6 month study comparing leflunomide with placebo and sulfasalazine
  - Study B9: 6 month extension of Study B8 (patients who received placebo in Study B8 received sulfasalazine in Study B9)
  - Study B10: 1 year study comparing leflunomide and MTX
  - Study B11: 1 year study comparing leflunomide with placebo and MTX.

One clinical study (3L01) was performed in the indication of PsA.

Three clinical studies were performed in the indication of juvenile rheumatoid arthritis (JRA).

Clinical trial exposure

Clinical trial exposure to leflunomide is based on data from a total of 16 studies.

During the clinical development program of leflunomide in the indication of RA, 1339 patients were exposed to the product in 11 clinical studies. Exposure data from these studies are presented in Table 9 to Table 13 below.

Exposure data from the study (3L01) performed in the indication of PsA is presented in Table 14 and Table 15 below.

An additional clinical study in the indication of RA, in which a total of 402 patients were exposed to leflunomide, was performed to compare two different maintenance doses of leflunomide. Exposure data from this study are summarized in Table 16.

Exposure data from the 3 studies in the indication of JRA, in which a total of 107 pediatric patients were exposed to leflunomide, are presented in Table 17 and Table 18 below.

Table 9 - Duration of exposure - Rheumatoid Arthritis (controlled and uncontrolled studies)

Rheumatoid Arthritis		
	Subjects	**Percentage**
Total population	**1339**	**100.0**
Duration of exposure		
≤28 days	46	3.5
29-84 days	106	8.0
85-168 days	161	12.2
169-252 days	87	6.6
253-336 days	86	6.5
>336 days	838	63.3

Note: Duration of treatment is calculated on a per subject basis, regardless of whether subjects continued treatment in an extension period.
Studies B1, B2, B3, B4, B5, B6, B7, B8, B9, B10 and B11.

Table 10 - Exposure by dose - Rheumatoid Arthritis (controlled and uncontrolled studies)

Rheumatoid Arthritis	
	Subjects
Total population	**1339**
Dose of exposure	
5 mg/day	129
10 mg/day	136
20 mg/day	816
25 mg/day	135
100 mg for 3 days (loading dose)	816
100 mg/week	24
200 mg/week	25

Note: Exposure by dose is presented on a per subject basis, regardless of whether subjects were exposed to more than one dose.
Studies B1, B2, B3, B4, B6, B8, B10 and B11. Studies B5, B7 and B9 not included as all 3 were extension studies at same dose.

Table 11 - Exposure by gender and age group - Rheumatoid Arthritis (controlled studies)

Rheumatoid Arthritis		
	Subjects	
	Number	**Percent**
Total population	**1116**	**100.0**
Females	844	75.6
Males	272	24.4
Adults (>18 and <65 years)	838	75.1

Rheumatoid Arthritis		
Elderly (≥65 years)	278	24.9

Controlled studies = Studies B3, B8, B9, B10 and B11.

Table 12 - Exposure by ethnic origin - Rheumatoid Arthritis (controlled studies)

Rheumatoid Arthritis		
	Subjects	
	Number	**Percent**
Total population	**1116**	**100.0**
White	1071	96.0
Black	22	2.0
Asian	4	0.4
Other	19	1.7

Controlled studies = Studies B3, B8, B9, B10 and B11.

Table 13 - Exposure in subgroups/special at-risk groups - Rheumatoid Arthritis (controlled and uncontrolled studies)

Rheumatoid Arthritis		
	Subjects	
	Number	**Percent**
Total subjects	**1339**	**100.0**
Previous DMARDs	914	68.3
Concomitant steroids	730	54.5
Hepatic impairment	16	1.2
Renal impairment	27	2.0
Hypertension	337	25.2
Ischemic heart disease	71	5.3
Diabetes mellitus	54	4.0
Concomitant NSAIDs	1137	84.9

Controlled and uncontrolled studies = Studies B1, B2, B3, B4, B5, B6, B7, B8, B9, B10 and B11.
DMARD: Disease Modifying Anti-Rheumatic Drug; NSAID: Non-Steroidal Anti-Inflammatory Drug.

Study 3L01 was conducted to support the indication of PsA. It was conducted in 31 centers in 9 countries from October 2000 to July 2002. A total of 95 patients were exposed to leflunomide during the study. All patients were exposed to the loading dose of 100 mg for 3 days followed by the maintenance dose of 20 mg, so data on exposure by dose are not presented for the study. Moreover, ethnic origin was not assessed during the study, so exposure by ethnic origin is also not presented.

Table 14 - Exposure by duration - Psoriatic Arthritis

Psoriatic Arthritis	
	Subjects
Total subjects	**95**
Duration of exposure	
1-14 days	1
15-28 days	3
29-56 days	8
57-98 days	16
99-126 days	5
127-168 days	21
>168 days	41

Note: If the date of last intake was unknown, the date of last visit was used instead. Source: Study 3LO1 report.

Table 15 - Exposure by gender and age - Psoriatic Arthritis

Psoriatic Arthritis		
	Subjects	
	Number	**Percent**
Total population	**95**	**100.0**
Females	40	42.1
Males	55	57.9
Age (years)		
Mean ± SD	48.6 ± 10.3	
Range	23-68	

Source: Study 3LO1 report.
SD: Standard Deviation.

Study 3012 was a randomized, double-blind, parallel-group comparison of two different maintenance doses of leflunomide, 10 mg and 20 mg, in the treatment of patients with RA. It was conducted in 62 centers in 12 countries.

Exposure data from this study are summarized by duration of exposure and demographic status in the table below.

Table 16 - Summary of exposure in Study 3012 by duration and demographic status - Rheumatoid Arthritis

Rheumatoid Arthritis			
Characteristic	**10 mg leflunomide (N = 202)**	**20 mg leflunomide (N = 200)**	**Total (N = 402)**
Duration			

Rheumatoid Arthritis			
Characteristic	**10 mg leflunomide (N = 202)**	**20 mg leflunomide (N = 200)**	**Total (N = 402)**
Mean (±SD) days	145.7 (±45.64)	155.3 (±37.22)	150.5 (±41.89)
No. (%) subjects treated for:			
<4 weeks	9 (4.5)	6 (3.0)	15 (3.7)
4 to <12 weeks	18 (8.9)	8 (4.0)	26 (6.5)
12 to <20 weeks	19 (9.4)	14 (7.0)	33 (8.2)
20 to <4 weeks	66 (32.7)	65 (32.5)	131 (32.6)
≥24 weeks	90 (44.6)	107 (53.5)	197 (49.0)
Gender			
Female (N, %)	163 (80.7)	172 (86.0)	335 (83.3)
Male (N, %)	39 (19.3)	28 (14.0)	67 (16.7)
Age			
<65 years (N, %)	151 (74.8)	162 (81.0)	313 (77.9)
≥65 years (N, %)	51 (25.2)	38 (19.0)	89 (22.1)
Ethnic origin			
Asian/Oriental	1 (0.5)	1 (0.5)	2 (0.5)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Multiracial	1 (0.5)	1 (0.5)	2 (0.5)
White	200 (99.0)	198 (99.0)	398 (99.0)

Source: Study 3012 report.
SD: Standard Deviation.

Study 1037 was conducted as an open-label pilot study to collect preliminary data on efficacy in order to determine whether therapy with leflunomide warranted further investigation in subjects with JRA. It was conducted in 7 centers in the US and Canada.

Study 3503 was a randomized, double-blind comparison of leflunomide and MTX in the treatment of patients with JRA. It was conducted in 32 centers in the US, Canada, New Zealand, Australia and Europe. It was followed by an extension period of 8 months, which was Study 3504.

Exposure data from these 3 studies are presented in Table 17.

Table 17 - Exposure by dose and duration - juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis			
Characteristic	**Uncontrolled pilot study (Study 1037) (N = 27)**	**Controlled study with open-label extension**	
		Double-blind phase Study 3503 (N = 47)	**Open-label Extension Study 3504 (N = 33)**

Juvenile rheumatoid arthritis			
Mean dose (mg)	12.5	11.5	11.5
Duration (days)			
Mean	154.25	114.9	337.8
Median	179	116	350
Range	7-210	28-154	171-532

Note: Dose was based on subject's body weight and, in Studies 3503 and 3504, could be adjusted at discretion of Investigator, so mean dose is presented.

Table 18 - Exposure by age and gender - juvenile rheumatoid arthritis

Juvenile rheumatoid arthritis			
Characteristic	**Uncontrolled pilot study (Study 1037) (N = 27)**	**Controlled study with open-label extension**	
		Double-blind phase Study 3503 (N = 47)	**Open-label Extension Study 3504 (N = 33)**
Mean age (years)	12.3	10.1	10.0
Range	6-17	3-17	3-16
Female (N, %)	23 (85.2)	35 (74.5)	27 (81.8)
Male (N, %)	4 (14.8)	12 (25.5)	6 (18.2)

In addition to the above-mentioned global clinical program, an international phase IIIb, double blind, double dummy, randomized study (LEFLU R 01143, LEADER) has been conducted between December 2007 and October 2009 in 121 randomized patients to assess the clinical efficacy response rate in patients with early RA treated with leflunomide, in two initial dosing treatment regimen groups (with and without loading dose). During the initial 3 day-double blind period, 2 parallel groups received either 20 mg or 100 mg of leflunomide with matching placebo. The 3-day double-blind period was followed by an open label maintenance period of 3 months, during which both groups received leflunomide 20 mg daily. The exposure by gender and age is presented in Table 19. The treatment exposure is presented in Table 20.

Table 19 - LEADER study: Demographic characteristics of the Intent-to-treat (ITT) population at baseline

	100 mg initial dose N = 54	**20 mg initial dose N = 66**	**TOTAL N = 120**
Gender			
Female	47 (87.0%)	48 (72.7%)	95 (79.2%)
Male	7 (13.0%)	18 (27.3%)	25 (20.8%)
Age (years)			
Mean (SD)	52.4 (12.4)	54.2 (14.0)	53.4 (13.3)
Median (range)	54.0 (24.78)	55.0 (28-79)	54.0 (24-79)

	100 mg initial dose N = 54	20 mg initial dose N = 66	TOTAL N = 120

Data are presented as absolute number (%) for the gender. Percentages refer to the total number in the column.
ITT: Intent-to-Treat; SD: Standard Deviation.

Table 20 - LEADER study: treatment exposure in the safety analysis population

	100 mg initial dose N = 54	20 mg initial dose N = 67	Total N = 121
Treatment duration (days)			
Mean ± SD	85.4 (16.5)	85.7 (16.9)	85.6 (16.6)
Median (range)	88 (14-124)	89 (7-120)	89 (7-124)

SD: Standard Deviation.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

The clinical development program for leflunomide, comprising a total of 11 clinical studies, as described in [Part II Module SIII], was completed in the late 1990s, and it is therefore not considered any more relevant to conduct a review of the exclusion criteria in those studies.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Leflunomide is marketed for more than 26 years. Therefore, the data form postmarketing exposure compensated for any limitations in the clinical trial development program in detecting adverse drug reactions (ADRs) in the exposed population.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 21 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	During the development program of leflunomide, limited data were generated concerning use in pregnant women. Recommendations in the summary of product characteristics (SmPC) for leflunomide with regard to pregnancy testing prior to initiation of treatment, use of contraception, and waiting period for women wishing to become pregnant and the washout procedure were based on the teratogenic and embryotoxic effects of leflunomide observed in animal toxicity studies (See [Part II Module SII]). However, given the higher incidence and prevalence of RA in women than in men as described in [Part II Module SI] and the potential risk of a female patient becoming pregnant despite the recommendations for reliable contraception during treatment and thereafter, it was decided that a specific post-approval study should be set up to collect data on pregnancy outcome and potential effects in infants in the event of inadvertent leflunomide exposure in the first trimester of pregnancy. The study [71] which uses a prospective cohort design was conducted by a network of teratogen counseling services located in the US and Canada, the Organization of Teratology Information Specialist (OTIS). The enrollment was initiated in 2000 and discontinued in Jun-2008. Pregnant subjects were recruited into one of three groups: women with a diagnosis of RA who took at least one dose of leflunomide (n = 64), a disease-matched comparison group without leflunomide exposure during pregnancy (n = 108), or a comparison group of healthy pregnant women (n = 78). The final report of the OTIS study, pregnancy outcomes for all 3 cohorts are shown in Table 21a.

Type of special population	Exposure

Table 21a - Pregnancy outcome in OTIS cohort study

	Group 1 Leflunomide exposed cohort	Group 2 RA cohort	Group 3 Non-disease cohort
Enrolled pregnancies	64	108	78
Live born N (%)	56 (87.5)	95 (88.0)[a]	72 (92.3)
Spontaneous abortion N (%)	5 (7.8)	8 (7.4)	3 (3.9)
Blighted ovum N (%)	1 (1.6)	0	0
Still birth N (%)	0	1 (0.9)	0
Elective termination N (%)	1 (1.6)	2 (1.9)	0
Lost to follow-up N (%)	1 (1.6)	2 (1.9)	3 (3.8)
Among live-born infants			
Preterm delivery <37 weeks gestation N (%)	20 (35.7)	23 (24.5)	5 (6.9)
Gestational age ± mean weeks (SD) (Range-weeks)	36.9 ± 3.2 (24.1 - 41.7)	38.2 ± 2.4 (26.4 - 41.4)	39.3 ± 1.5 (33.9 - 41.6)
Birth Size – full-term infants			
Birth Weight ± mean g (SD) Birth Length ± mean cm (SD) Birth Head Circumference ± mean cm (SD)	3116 ± 457 50.0 ± 2.4 34.1 ± 1.6	3310 ± 391 50.4 ± 2.6 34.3 ± 1	3580 ± 420 51.2 ± 2.3 34.6 ± 1.4
Structural defects			
Major structural defects N (%)	3 (5.4)[b]	4 (4.2)[c]	3 (4.2)[d]
Functional problems	1 (1.6) Hydronephrosis. 1 (1.6) bilateral vesicoureteral reflux	1 (0.9) Hydronephrosis. 1 (0.9) bilateral vesicoureteral reflux with unilateral duplicated collecting system	1 (1.7) congenital esotropia 1 (1.7) neonatal encephalopathy and seizures secondary to subarachnoid bleed. 1 (1.7) tracheomalacia.
Defects noted in spontaneous abortions or elective terminations	0	3	0

Type of special population	Exposure
	Structural defects in all pregnancies n/N (%) excluding lost to follow-up: 3/63 (4.8) | 7/106 (6.6) | 3/75 (4.0) *a* 1 neonatal death in group 2 due to necrotizing enterocolitits. *b* N = 3: occult spinal dysraphism (1), multicystic kidney disease (1), microcephaly (1). *c* N = 4: patent foramen ovale with peripheral pulmonic stenosis (1), atrial septum defect with pulmonic valve stenosis (1), bilateral inguinal hernia and microcephaly (1), and posterior chamber of left eye did not form correctly and caused posterior lacrimal cataract, required surgery (1). *d* N = 3: cryptorchidism (1), Kleppel-Trenauny syndrome (1) and vocal cord paralysis (1). OTIS: Organization of Teratology Information Specialist; RA: Rheumatoid Arthritis; SD: Standard Deviation. Based on the data presented above, the proportion of pregnancies with adverse outcomes is comparable between the leflunomide-exposed cohort and the disease-matched comparison group. Furthermore, no specific patterns of major structural defects or minor anomalies were noted in the leflunomide-exposed infants, nor were the reported congenital anomalies consistent with those noted in animal developmental toxicity studies. The results of this study, which was prematurely discontinued due to a decline in recruitment, do not change the initial contraindication of leflunomide use in pregnancy. In particular, the study did not address possible risks associated with use of leflunomide over the entire period of embryonic development as all subjects in the leflunomide exposed group discontinued the medication upon recognition of pregnancy, nearly all went through at least one course of drug elimination procedure and most subjects were not exposed to leflunomide beyond 3 weeks post conception. A second publication [72] from the OTIS cohort study provided pregnancy outcomes in women not enrolled in the main cohort (16 women exposed to leflunomide during pregnancy and 29 women exposed preconception), 2 major structural defects were reported in women exposed during pregnancy and no malformations reported in women exposed preconception. As of 10-Sep-2013, approximately 1093 pregnancy exposures have been identified. For adverse events of specific interest under Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Congenital, familial and genetic disorders, SMQ Neonatal disorders, SMQ Pregnancy and Neonatal topics and specific relevant preferred term (PT) terms, there are 49 cases of Congenital, familial, and genetic disorders, 83 cases of spontaneous abortions, 2 cases reporting stillbirth, 3 cases of ectopic pregnancy, 43 premature births, 1094 pregnancy and neonatal topics, and 49 male mediated cases Reported outcome of female pregnancy exposure cases ascertained retrospectively or prospectively can differ considerably. All preterm births and congenital malformations were reported retrospectively, and all spontaneous abortions were also reported retrospectively. In contrast, cases ascertained prospectively were live births or elective terminations. Retrospective ascertainment is subject to reporting bias and cannot be used to estimate increased risk of preterm births, congenital malformations or spontaneous abortions. There were no frank congenital malformations reported to Sanofi. Of-note, the structural defects reported to date represent isolated reports and do not reveal a pattern of defects.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities	• Renal impairment:

Type of special population	Exposure
• Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Leflunomide was administered as a single oral 100 mg dose to 3 haemodialysis patients and 3 patients on continuous peritoneal dialysis (CAPD). The pharmacokinetics of A771726 in CAPD subjects appeared to be similar to healthy volunteers. A more rapid elimination of A771726 was observed in haemodialysis subjects which was not due to extraction of medicinal product in the dialysate. • Hepatic impairment: No data are available regarding treatment of patients with hepatic impairment. The active metabolite A771726 is extensively protein bound and cleared via hepatic metabolism and biliary secretion. These processes may be affected by hepatic dysfunction.
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable
Other • Children	Three clinical studies were performed on leflunomide in the indication of Juvenile RA. The exposure data is provided in [Part II Module SIII]. A total of 107 paediatric patients were exposed to leflunomide in the context of these studies. The results of these trials have been included in the European SmPC; however, the efficacy and safety of the product have not been established in this population.

CAPD: Continuous Peritoneal Dialysis; MedDRA: Medical Dictionary for Regulatory Activities; OTIS: Organization of Teratology Information Specialist; PT: Preferred Term; RA: Rheumatoid Arthritis; SD: Standard Deviation; SmPC: Summary of Product Characteristics; SMQ: Standardized MedDRA Query.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1. Method used to calculate exposure

The Marketing Authorization Holder (MAH) is currently utilizing the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience since December 2019. The MARCO application collects data monthly, as a result, the data may not correspond precisely to the current reporting interval.

Methodology:

- Total sales in mg were calculated by multiplying counting units for tablets with their respective strength in mg.
- Total patient years were estimated by dividing total sales in mg with World Health Organization (WHO) defined daily dose (DDD) of 20 mg for oral formulations and then dividing it with 365.

SV.1.2. Exposure

Cumulative patient exposure during 18 years and 8 months period:

Exposure from the cumulative experience is available from MARCO[1] for the period from 01 January 2006 through 31 August 2024.

Based on the above methodology, the cumulative exposure to leflunomide could be estimated to be 4.4 million patient years.

Detailed usage data are not available therefore presentation of sales data by age, sex, and indication is not possible. The usage data is only presented by formulation strength.

Table 22 - Leflunomide Worldwide Sales-Sanofi 01-Jan-2006 to 31-Aug-2024[a] In Units

	LEFLUNOMIDE			
	TABLET			
Worldwide Sales	10 mg	100 mg	100 mg + 20 mg[b]	20 mg
Total sales in units	396 829 459	2 544 486	19 998	1 405 509 887
Total sales in mg	3 968 294 589	254 448 563	-	28 110 197 748
Grand total sales in mg	32 332 940 900			

[1] Due to MARCO database updates performed on 01 February 2022 sales data before 01 January 2006 are no more available in MARCO database and sales volume after 01 January 2006 could decreased due to these updates.

	LEFLUNOMIDE			
	TABLET			
Worldwide Sales	**10 mg**	**100 mg**	**100 mg + 20 mg**[b]	**20 mg**
Grand total sales in mg (in million)	32 332.9			
WHO DDD in mg	20			
Total patient days in million	1616.6			
Total patient-years in million	4.4			

a Sales data is available from Jan-2006 in MARCO database.

b The strength 100 mg + 20 mg corresponds to combination INN, hence, excluded from the patient exposure.

Units:

Tablets: Total number of Tablets.

Source: MARCO database (update 23-Oct-2024).

DDD: Defined Daily Dose; INN: International Nonproprietary Name; MARCO: Margin Consolidated; WHO: World Health Organization.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Non-clinical and clinical data, as well as postmarketing experience, do not demonstrate a significant risk of misuse 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

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

This section is not applicable as the initial RMP for leflunomide was submitted prior to the implementation of GVP Module V revision 2.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

The following changes or reclassification are proposed in RMP v6.0:

The EU-RMP version 6.0 is updated in order to comply with the current regulation, specifically guideline on GVP Module V revision 2. The important identified risks “Hepatic reactions”, “Blood cytopenia” and “Infections” are withdrawn based on the newly revised GVP Module V definitions; these risks being well characterized based on extensive safety experience and well managed through current medical practice.

In Pharmacovigilance Risk Assessment Committee (PRAC) PSUR assessment report (Procedure no.: EMEA/H/C/PSUSA/00001837/202309) the following request/recommendation was received:

“The MAH of the innovator product is requested to discuss the effectiveness and usefulness of the aRMM specifically related to the safety concerns hepatic reactions, blood cytopenia and infections and to discuss the need for maintaining latter safety concerns in the RMP.

Based on this discussion, the MAH may propose removal of part of the key-messages of the aRMM and removal of part of the safety concerns in the RMP to be submitted in a specific variation.”

Marketing Authorization Holder discussion:

There is currently no global effectiveness and/or usefulness evaluation established for leflunomide’s risk minimization measures (RMMs). Additional risk minimization measures including educational tools for healthcare professionals (HCPs) and patients, along with an ad hoc information service, have been implemented.

The safety analysis in the previous periodic benefit risk evaluation reports (PBRERs) along with routine signal monitoring and pharmacovigilance activities have revealed no new information

regarding the hepatic reactions, blood cytopenia and infections risks in context of seriousness, frequency and severity; under recommended conditions of use as indicated in the reference safety information (RSI). These three risks are adequately addressed in the RSI. A recent review of postmarketing data in the context of PBRER covering the period from 11 September 2023 through 10 September 2024 identified no new safety information necessitating changes to the risk characterization for hepatic reactions, blood cytopenia, or infections. The safety evaluation indicates no changes to the established safety profile of leflunomide. Routine pharmacovigilance activities, as defined by the MAH and deemed sufficient for evaluating the aRMMs, did not reveal any risks beyond those identified in the EU SmPC.

Leflunomide's safety profile is well-defined, based on 26 years of postmarketing experience, with no changes observed. Current product labeling provides comprehensive information to mitigate the risks of hepatic reactions, blood cytopenia, and infections. Consequently, the MAH agrees to remove these risks from the key messages of the aRMM within the RMP. These risks will continue to be monitored through routine pharmacovigilance activities.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for leflunomide:

- Important identified risk:
  - Teratogenicity
- Important potential risk:
  - Male-mediated fetal toxicity
  - Progressive multifocal leukoencephalopathy (PML)
- Missing information:
  - None

SVII.3.1. Presentation of important identified risks and important potential risks

Table 23 - Important identified risk: Teratogenicity

Important identified risk	**Teratogenicity**
Potential mechanism	Unknown. Animal toxicity tests demonstrated that A771726, the main metabolite of leflunomide, is teratogenic and embryotoxic in rats and rabbits.
Evidence source(s) and strength of evidence	Non-clinical data, clinical data, postmarketing experience. [73]
Characterization of the risk	Frequency with 95% CI: In the publication of the main analysis from the OTIS cohort study, [73] major structural defects were reported in 3 of 56 live-born infants whose mothers were exposed to leflunomide in early pregnancy, corresponding to a frequency of 5.4%. While this rate is higher than that in infants whose mothers had a diagnosis of RA but who were not treated with leflunomide (4.2%), it should be interpreted with caution since the estimate rate is based on a small sample size of only 56 live-births and is not statistically significantly different from the

Important identified risk	Teratogenicity
	rate in the disease-matched comparison cohort (P = 0.669). Moreover, the defects noted in the leflunomide-exposed cohort, ie, occult spinal dysraphism, multicystic kidney disease, and microcephaly, do not appear to be consistent with the reproductive toxicity data in animals. A second publication [74] from the OTIS cohort study provided pregnancy outcomes in women not enrolled in the main cohort (16 women exposed to leflunomide during pregnancy and 29 women exposed preconception), 2 major structural defects were reported in women exposed during pregnancy and no malformations reported in women exposed preconception. Severity and nature of risk: Animal toxicity tests demonstrated that A771726, the main metabolite of leflunomide, is teratogenic and embryotoxic in rats and rabbits. Seriousness/outcomes: The potential teratogenic effect of leflunomide may manifest as major structural defects. Background incidence/prevalence: Rheumatoid Arthritis: Major birth defects occurred at a rate of 4.2% of live-births to women with RA who did not use leflunomide. No data is available in the literature for prevalence. Psoriatic arthritis: Data regarding teratogenicity in patients with PsA is very limited in the literature. In patients with inflammatory arthropathies treated with TNF therapy, no increased risk of embryotoxicity or teratogenicity, or adverse pregnancy outcome (such as birth defects, premature birth, and low birth weight) has been reported as compared with the general population. [75] No data is available in the literature for prevalence. Impact on individual patient: Potential emotional distress, impact would depend on continuation or interruption of therapy.
Risk factors and risk groups	No particular risk groups or risk factors have been identified.
Preventability	• Contraindication in pregnant women and women of childbearing potential who are not using reliable contraceptive methods. • Application of the washout procedure, checked by monitoring plasma levels, followed by an appropriate waiting period before starting pregnancy.
Impact on the risk-benefit balance of the product	There is no deleterious impact on the benefit-risk balance anticipated for leflunomide.
Public health impact	Not evaluated

CI: Confidence Interval; OTIS: Organization of Teratology Information Specialist; P: Probability; PsA: Psoriatic arthritis; RA: Rheumatoid Arthritis; TNF: Tumor Necrosis Factor.

Table 24 - Important potential risk: Male-mediated fetal toxicity

Important potential risk	Male-mediated fetal toxicity
Potential mechanism	The mechanism of action of leflunomide involves interference with de novo pyrimidine synthesis and affects rapid cell division during spermatogenesis.
Evidence source(s) and strength of evidence	Non-clinical data.
Characterization of the risk	Frequency with 95% CI: Not known

Important potential risk	Male-mediated fetal toxicity
	Severity and nature of risk: Although there are no specific data on the risk of male-mediated fetal toxicity, and no animal studies have been performed specifically to evaluate this potential risk, there is a possibility that the use of leflunomide may lead to marginal (reversible) decreases in sperm concentration, total sperm count and rapid progressive motility. Seriousness/outcomes: Not known Background incidence/prevalence: No data regarding the male-mediated fetal toxicity in patients with either RA or PsA is available in the literature. Impact on individual patient: Not known
Risk factors and risk groups	Not known
Preventability	The potential risk of male-mediated fetal toxicity associated with the use of leflunomide can be minimized by following the recommendations for reliable contraception during treatment and for discontinuing leflunomide and applying the washout procedure, checked by monitoring plasma levels, and appropriate waiting period.
Impact on the risk-benefit balance of the product	There is no deleterious impact on the benefit-risk balance anticipated for leflunomide.
Public health impact	Not evaluated

CI: Confidence Interval; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis.

Table 25 - Important potential risk: Progressive multifocal leukoencephalopathy (PML)

Important potential risk	Progressive multifocal leukoencephalopathy (PML)
Potential mechanism	Reactivation of John Cunningham (JC) polyomavirus in immunocompromised hosts.
Evidence source(s) and strength of evidence	Published case report, postmarketing experience.
Characterization of the risk	Frequency with 95% CI: Not known. Severity and nature of risk: Progressive multifocal leukoencephalopathy is a rare but severe disorder characterized by progressive neurologic deterioration due to reactivation of JC polyomavirus in immunocompromised hosts. Seriousness/outcomes: Serious including hospitalization, life threatening might have fatal outcome. Impact on individual patient: Life threatening/Fatal.
Risk factors and risk groups	• Recent or concurrent treatment with immunosuppressive agents such as rituximab, infliximab, azathioprine and underlying systemic lupus erythematosus (SLE). • The risk could be higher in immunocompromised patients.
Preventability	Stop the treatment immediately in case of suspicion of PML and initiate washout procedures

Important potential risk	Progressive multifocal leukoencephalopathy (PML)
Impact on the risk-benefit balance of the product	There is no deleterious impact on the benefit-risk balance anticipated for leflunomide.
Public health impact	Not evaluated

CI: Confidence Interval; HIV: Human Immunodeficiency Virus; JC: John Cunningham; PML: Progressive Multifocal Leukoencephalopathy; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis; SLE: Systemic Lupus Erythematosus.

SVII.3.2. Presentation of the missing information

Not applicable

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 26 - Summary of the safety concerns

Important identified risk	Teratogenicity
Important potential risk	Male-mediated fetal toxicity
	Progressive multifocal leukoencephalopathy (PML)
Missing information	None

PML: Progressive Multifocal Leukoencephalopathy.

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

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of leflunomide.

The safety profile of leflunomide will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities planned for this product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities ongoing or planned for leflunomide.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for leflunomide.

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

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 27 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Teratogenicity	**Routine risk communication:** • Labelled in Sections 4.3 and 4.6 of the SmPC • Labelled in Section 2 of package leaflet (PL) **Routine risk minimization 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 minimization measures beyond the Product Information:** Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA.
Male-mediated fetal toxicity	**Routine risk communication:** • Labelled in Sections 4.4 and 4.8 of the SmPC • Labelled in Section 2 of PL **Routine risk minimization 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 minimization 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:** • Labelled in Section 4.4 of the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization 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.

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

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 28 - Additional risk minimization 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: teratogenicity and male-mediated fetal toxicity.
Rationale for the additional risk minimization activity	• 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
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 (ie, 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 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 minimization 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 of plasma leflunomide levels.
Rationale for the additional risk minimization 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 (through Physician Leaflet) for the testing of plasma leflunomide levels, 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 (ie, website, email).
Plans to evaluate the effectiveness of the	Routine Pharmacovigilance activities.

interventions and criteria for success	

RMP: Risk Management Plan.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 29 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Teratogenicity	**Routine risk minimization measures:** • SmPC Sections 4.3 and 4.6 • PL Section 2 • Recommendations for women of childbearing potential to use effective contraception in SmPC Section 4.4 and PL Section 2 • Legal status of prescription: Restricted distribution of leflunomide with initiation and supervision of treatment by a specialist experienced in the therapeutic management of RA and PsA **Additional risk minimization measures:** • Educational tools 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
Male-mediated fetal toxicity	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimization 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 minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

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

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Arava (Leflunomide)

This is a summary of the RMP for Arava. The RMP details important risks of Arava, how these risks can be minimized, and how more information will be obtained about Arava's risks and uncertainties.

Arava's SmPC and its PL give essential information to HCPs and patients on how Arava should be used.

This summary of the RMP for Arava 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 Arava's RMP.

I. 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) 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 EMA website, under the medicine's webpage:

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

II. 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 below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 aRMMs mentioned under relevant important risks, outlined below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR 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 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 30 - List of important risks and missing information

Important identified risk	Teratogenicity
Important potential risks	Male-mediated fetal toxicity
	Progressive multifocal leukoencephalopathy (PML)
Missing information	None

PML: Progressive Multifocal Leukoencephalopathy.

II.B. SUMMARY OF IMPORTANT RISKS

Table 31 - 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. [73]
Risk factors and risk groups	No particular risk groups or risk factors have been identified.

Teratogenicity	
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 32 - Important potential 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 known
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 33 - Important potential 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

Progressive multifocal leukoencephalopathy (PML)	
	Additional risk minimization measures: None

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

II.C. POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.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.

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

There are no studies required for Arava.

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PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Additional risk minimization measures (aRMMs) 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 two safety concerns (teratogenicity and male mediated fetal toxicity) 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 aRMMs

1. **<u>Educational tools for Physician</u>:**

Physician Leaflet:

- Relevant information of the safety concern(s) addressed by the aRMM

  The most important risks you should be aware of when prescribing Arava® include:

  - Risk of serious birth defects when administered during pregnancy.

- 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 Arava 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 Arava, A771726 is suspected to cause serious birth defects when administered during pregnancy. Therefore, Arava 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/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 Arava should be guaranteed.
  - o For men wishing to father a child, the same wash-out procedure as recommended for women should be considered.
  - o Between the first occurrence of a plasma concentration below 0.02 mg/L and fertilization, a waiting period of 3 months is required.
  - o Ad hoc advisory service: An ad hoc advisory service is available for providing information on leflunomide plasma level testing for patients treated with Arava. Please contact sanofi-aventis company to obtain further information concerning this service (Internal note: local phone number 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 Arava.
- The wash-out procedure is recommended to accelerate A771726 elimination, when its needs to be cleared rapidly from the body.

2. <u>Educational tool for Patient</u>:

Patient Information Sheet:

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

- Precautions of use for Arava

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

- Arava wash-out procedure

After discontinuing Arava, 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 Arava 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 Arava levels are still too high, a repeated drug wash-out procedure may be necessary.

When it is confirmed that Arava 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 Arava passes into semen, reliable contraception during treatment with Arava should be guaranteed.

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

When it is confirmed that Arava 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.