Arava

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IA/0086	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	06/08/2024		SmPC and PL	
PSUSA/1837/ 202309	Periodic Safety Update EU Single assessment - leflunomide	30/05/2024	01/08/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1837/202309.
IA/0085	B.I.b.1.d - Change in the specification parameters	23/04/2024	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IA/0084	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	28/02/2024	n/a		
N/0082	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2023	01/08/2024	PL	
IB/0081	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/08/2022	n/a		
IB/0079	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	25/03/2022	12/08/2022	SmPC and PL	Update of Sections 4.4 and 4.8 of the SmPC with information on skin ulcer following PRAC recommendation issued for the Post-Authorisation Measure EMEA/H/C/000235/LEG/058.1 for leflunomide containing products. The PL has been updated accordingly.
IA/0080/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	25/02/2022	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
N/0078	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2021	12/08/2022	PL	
IG/1386	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	03/08/2021	12/08/2022	Annex II and PL	
PSUSA/1837/ 202009	Periodic Safety Update EU Single assessment - leflunomide	06/05/2021	n/a		PRAC Recommendation - maintenance
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/10/2020	12/08/2022	PL	
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/02/2020	12/08/2022	PL	
PSUSA/1837/ 201709	Periodic Safety Update EU Single assessment - leflunomide	12/04/2018	n/a		PRAC Recommendation - maintenance
N/0073	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2018	30/07/2018	Labelling and PL	
IG/0823	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/07/2017	30/07/2018	SmPC and PL	
PSUSA/1837/ 201609	Periodic Safety Update EU Single assessment - leflunomide	06/04/2017	n/a		PRAC Recommendation - maintenance

IA/0069	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	03/06/2016	n/a		
N/0068	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2016	15/09/2016	PL	
PSUSA/1837/ 201509	Periodic Safety Update EU Single assessment - leflunomide	14/04/2016	n/a		PRAC Recommendation - maintenance
IG/0635	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2015	15/09/2016	SmPC and PL	
WS/0816/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/10/2015	15/09/2016	SmPC, Annex II and PL	
PSUSA/1837/ 201409	Periodic Safety Update EU Single assessment - leflunomide	10/04/2015	n/a		PRAC Recommendation - maintenance
WS/0560/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/09/2014	07/11/2014	SmPC and PL	With the development of teriflunomide, the main active metabolite of leflumonide, as a drug for the treatment of multiple sclerosis, several interaction studies were performed according to current standards. This variation

	This worksharing includes 9 type II variations per product grouped as follows: -Type II variation, C.I.4 : Update of sections 4.3 and 4.4 of the SmPC contraindicating and including a warning on teriflunamide the active metabolite of leflunomide; -2 Type II variations, C.I.4 : Update of section 4.5 of the SmPC for leflunomide related to the study reports HWA486/1032/001 (interaction cimetidine) and -HWA486/2F0.1 (interaction with methotrexate); - 6 Type II variations, C.I.4 : Update of section 4.5 of the SmPC for teriflunomide related to the following Study reports INT11697-INT11720-INT12503-INT12500-INT10564-INT6040. In addition and following CHMP request section 4.4 of the SmPC was updated to include a warning for patients to be evaluated for tuberculosis before starting treatment with leflunomide. The PL was revised to reflect the above warnings and interactions. Furthermore, the MAH took the opportunity of this worksharing to reflect the interaction studies in the RMP and to include DRESS syndrome in the RMP as requested by PRAC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				hamonised the results of the interaction studies of the main metabolite with the parent drug leflumonide. Caution and intensified monitoring is recommended for combined use of leflunomide and a broad range of products since the plasma levels may be increased by the concurrent use of leflumonide. The benefit/risk balance of leflumonide remains positive, considering that interactions could be controlled by dose adjustments. Co administration of teriflunomide with leflunomide is not recommended, as leflunomide is the parent compound of teriflunomide.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0454	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	17/07/2014	n/a		
WS/0526	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order	22/05/2014	07/11/2014	SmPC and PL	14 cases of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) have been retrieved. 10 cases are reports from literature articles and 4 are spontaneous. Of the 14 cases, 7 provide insufficient or inconclusive information. The remaining 7 spontaneous and literature

	to add a warning and update the safety information on DRESS (drug reaction with eosinophilia and systemic symptoms). The section 2 and 4 of the Package Leaflet were proposed to be updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives for Finland, Malta, Sweden and United Kingdom in the Package Leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				cases of DRESS have (strong) suggestive evidence and strong temporal association with leflunomide (2 “definite” and 5 “possible” cases according to the RegiSCAR criteria). The product information has therefore been updated to include that cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in patients treated with leflunomide. The MAHs of generic products containing leflunomide will update their product information in line with that of the reference product.
PSUSA/1837/ 201309	Periodic Safety Update EU Single assessment - leflunomide	10/04/2014	n/a		PRAC Recommendation - maintenance
IA/0060	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/02/2014	n/a		
IG/0354	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/11/2013	07/11/2014	SmPC and PL	
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		
WS/0271	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC to add cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis and warn physicians about these	15/11/2012	18/12/2012	SmPC and PL	Based on published clinical trial data and single case reports in the scientific literature, a possible causal association of leflunomide treatment with worsening of underlying psoriasis and pustular psoriasis is strongly suggested by two cases identified from the company global pharmacovigilance database reporting positive rechallenge after reintroduction of leflunomide. No similar published

	skin reactions. The PL is being updated accordingly. Furthermore, the list of local representatives in section 6 of the PL is being updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				reports were identified during a comprehensive review of the scientific literature. Based on these observations, it can be concluded that leflunomide therapy may be associated with paradoxical worsening of underlying psoriasis and occurrence of pustular psoriasis. A possible causal association of leflunomide treatment with cutaneous lupus erythematosus is strongly suggested by one case identified from the company global pharmacovigilance database and published in the scientific literature reporting a positive rechallenge of cutaneous lupus erythematosus after reintroduction of leflunomide. Such causal relation is further supported by 5 additional cases identified from the company global pharmacovigilance database and 1 additional report from the scientific literature review documenting plausible time to onset and positive dechallenge in the absence of other obvious confounders except for the underlying autoimmune disease. Cutaneous lupus erythematosus was largely reversible with discontinuation of leflunomide with or without a drug elimination procedure and, in some cases, with the administration of corrective treatment. Based on these findings it can be concluded that leflunomide therapy may be associated with the development of cutaneous lupus erythematosus. Overall, based on the presented data, cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis are added to the SmPC as new adverse events with a “not known” frequency. The CHMP also required that Physicians be warned in section 4.4 that pustular psoriasis and worsening of psoriasis have been reported after the use of leflunomide and that treatment withdrawal may be considered taking into account patient’s disease and past

					history.
IA/0055/G	This was an application for a group of variations. B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/03/2012	n/a		
II/0050	Update of section 4.4 of the SmPC to strengthen the warning regarding peripheral neuropathy. The PIL is updated accordingly. Furthermore, changes relating to the implementation of the latest QRD template are being proposed. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	19/03/2012	SmPC, Annex II, Labelling and PL	Peripheral neuropathy (PNP) has been associated with autoimmune diseases like RA; however, there are also signals from the literature and the Company's Safety Database indicating a causal relationship between the occurrence of PNP and the use of leflumonide. From the submitted data it may be concluded that leflunomide is an independent risk factor for PNP besides other risk factors and it is considered relevant to inform prescribers regarding this risk. Based on the available safety data from case reports and several non-randomized cohort studies, a warning regarding the association of leflunomide use and PNP has been added and the frequency of PNP in section 4.8 has been updated to "common".
IG/0147/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons	29/02/2012	n/a		

	or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0049	Update of section 4.4 of the SmPC regarding the risk of leflunomide use in combination with biologicals following the CHMP assessment of the COLEBI study. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	22/09/2011	10/11/2011	SmPC	The COLEBI study is a retrospective observational study comparing RA patients who were treated with a combination of leflunomide + TNF-inhibitor with those who were treated with a combination of MTX + TNF-inhibitor. Following the assessment of the results of the COLEBI study, which have been submitted as a follow-up measure, the MAH was asked to update the warning section of the SmPC to with regard to the combined use of leflunomide and TNF-Inhibitors. Furthermore, the warning section has been updated regarding the risk of tuberculosis and the need for appropriate testing.
II/0047	Update of sections 4.2 and 5.1 of the SmPC to reflect the outcome of the clinical study R01143 (LEADER) regarding the use of a loading dose, as requested by the CHMP. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article	23/06/2011	10/08/2011	SmPC	The MAH has conducted a post-marketing study (R01143, LEADER) in which two initial dosing regimen were used, 121 DMARD-naive patients with early RA were randomized to receive either the 20 mg or 100 mg starting dose in a double-blind, double-dummy fashion, followed by an open-label maintenance period of 3 months during which 20mg/d where administered. The ACR20 response rate at 90 days (primary endpoint) was statistically significantly higher in

	45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				the flat-dose group compared to the loading dose group. There were, however, no significant differences for any of the secondary efficacy parameters, such as ACR50 or DAS28 response and, also considered the small sample size, superiority of flat dosing regimen above the 100 mg loading dose cannot be concluded. However, there appears to be no loss of clinical response in the flat dose regimen as compared to the loading dose regimen. The incidence of gastrointestinal AEs and of elevated liver enzymes reported as adverse events tended to be higher during the earlier phases of treatment in patients receiving the loading dose of 100 mg leflunomide. Overall, the safety data obtained were consistent with the known safety profile of leflunomide.
IG/0091	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	05/07/2011	n/a		
II/0048	Update of 4.4 of the SmPC to amend the warning for interstitial lung disease (ILD) as requested by the CHMP. The PIL was revised accordingly. In addition the description of the risk of teratogenicity in the PIL was aligned with the educational material agreed in August 2010. Further updates concerns the Annex IIB regarding DDPS / RMP version and the implementation of the latest QRD template. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article	17/03/2011	18/04/2011	SmPC, Annex II and PL	Following a CHMP request, the MAH conduct a search of recent relevant literature on interstitial lung disease (IDL) in association with leflunomide treatment as a follow-up measure. Following the assessment of the information provided by the MAH, an update of section 4.4 of the SmPC was requested to highlight the increased risk in case of pre-existing IDL. Furthermore, the MAH has aligned the information on serious birth defects in the package leaflet with the Patient Sheet (educational material) of the EU-RMP.

	45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				
IG/0004/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	06/05/2010	n/a	Annex II	
II/0046	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	18/02/2010	29/04/2010	SmPC, Labelling and PL	
II/0045	Update of the Annex II with the new version number of the adopted DDPS (version 2.4) and the RMP	17/12/2009	27/01/2010	Annex II	The MAH has submitted an updated description of the Pharmacovigilance System and an RMP to harmonise these

	(version 1.3). Update of or change(s) to the pharmaceutical documentation				documents with those recently approved for Leflunomide Winthrop. The documents are identical. The conditions for the marketing authorisation (Annex II) have also been updated in accordance with those agreed upon for Leflunomide Winthrop.
II/0043	Update of section 4.6 of the SPC based on conclusions from the OTIS study. This variation application is submitted further to the request of the CHMP following assessment of PSUR 19-20 for Arava, covering the period 11 Septmeber 2007 - 10 September 2008. The MAH has also taken the opportunity, for consistency with the SPC, to include minor changes in section 6 "Further information" of the package leaflet for the strengths 10 mg and 100 mg. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	28/10/2009	SmPC and PL	The MAH was requested to update the SPC section 4.6 based on conclusions from the organisation of teratology information specialists (OTIS) study. In this study it was shown that there was no increased risk of malformations after exposure to leflunomide in the first three weeks of pregnancy and followed by a drug elimination procedure. Although reassuring for women who become inadvertently pregnant while taking leflunomide, these results are too limited to warrant the removal of the contraindication for pregnancy.
IA/0044	IA_37_a_Change in the specification of the finished product - tightening of specification limits	11/08/2009	n/a		
R/0041	Renewal of the marketing authorisation.	23/04/2009	01/07/2009	SmPC, Annex II, Labelling and PL	
IA/0042	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	11/03/2009	n/a		
IB/0039	IB_25_a_01_Change to comply with Ph. - compliance with EU Ph. - active substance	15/05/2008	n/a		

IA/0040	IA_05_Change in the name and/or address of a manufacturer of the finished product	23/04/2008	n/a	Annex II and PL	
II/0038	Update of Summary of Product Characteristics, Labelling and Package Leaflet To align the Product Information to the latest EMEA/QRD template (version 7.2) and to amend the PL to reflect the results of the user testing. Furthermore, the Marketing Authorisation Holder took the opportunity to update Annex II to reflect the submission of yearly PSURs and to include the prescription status ("Medicinal product subject to medical prescription") on the label of the bottles. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2008	26/02/2008	SmPC, Annex II, Labelling and PL	The Product Information was updated in order to be in line with the latest EMEA/QRD template (version 7.2). In this respect section 4.8 of the SPC was reviewed according to the current Guideline on Summary of Product Characteristics (October 2005) in order to describe the adverse reactions according to MedDRA system organ class and to rank them under headings of frequency using the convention as stated in the Guideline and in the EMEA/QRD template. Furthermore, the PL was updated to reflect the results of the user testing. Finally, the Marketing Authorisation Holder took the opportunity to update Annex II to reflect the submission of yearly PSURs and to include the prescription status ("Medicinal product subject to medical prescription") on the label of the bottles.
II/0034	Update of section 4.8 of the SPC to include the adverse reaction "renal failure" (with unknown frequency). Section 4 of the PL was updated accordingly. Additionally, the Marketing Authorisation Holder took the opportunity to update the list of local representatives in section 6 of the PL and to replace "cholestyramine" with the INN name "colestyramine" in the SPC and PL. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	08/11/2007	SmPC and PL	In the framework of the assessment of PSURs No 16 and 17, covering the period from 11 March 2006 to 10 March 2007, the CHMP requested the Marketing Authorisation Holder to provide a cumulative review for renal failure. A total of 139 cases were reported. The global exposure was more than 1 million patients per year. Although the reporting rate of renal failure remained rare, the CHMP noted that there were more than 100 reported cases for renal failure from which most were serious. Therefore, the CHMP concluded that a possible causal relationship between leflunomide and renal failure can not be excluded. Thus, sections 4.8 of the SPC and 4 of the PL were updated to include "renal failure", with unknown frequency.

					Additionally, the Marketing Authorisation Holder took the opportunity to update the list of local representatives in section 6 of the PL and to replace "cholestyramine" with the INN name "colestyramine" in the SPC and PL.
IB/0037	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	07/11/2007	n/a		
IB/0036	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	07/11/2007	n/a		
IB/0035	IB_30_b_Change in supplier of packaging components - replacement/addition	17/10/2007	n/a		
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/01/2007	n/a	PL	
IA/0032	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	04/08/2006	n/a		
II/0029	This variation relates to an update of section 4.8 "Undesirable effects" of the Summary of Product Characteristics and section 4 "Possible side effects" of the Package leaflet for Arava to include "cutaneous necrotizing vasculitis" following a review of the available safety information. Update of Summary of Product Characteristics and Package Leaflet	17/11/2005	10/01/2006	SmPC and PL	Following the receipt of isolated postmarketing reports of necrotising cutaneous vasculitis, a cumulative search of the MAH's database was performed for vasculitis and specifically vasculitis necrotising. After the review of the available safety information, the MAH decided to amend the Company Core Data Sheet (CCDS) to include the description of the specific potential risk of 'cutaneous necrotizing vasculitis'. In line with this the MAH has proposed to amend the Summary of Product Characteristics and the Package leaflet to include "necrotising cutaneous vasculitis" as a very rare undesirable effect.

IA/0031	IA_01_Change in the name and/or address of the marketing authorisation holder	16/12/2005	n/a	SmPC, Labelling and PL	
IA/0030	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/12/2005	n/a	Annex II and PL	
II/0028	This variation relates to an update of sections 4.2 "Posology and method of administration", 5.1 "Pharmacodynamic properties" and 5.2 "Pharmacokinetic properties" of the Summary of Product Characteristics to include the results of clinical studies in patients with polyarticular Juvenile Rheumatoid Arthritis (JRA). Consequent changes are proposed in section 3 "How to take Arava" of the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	13/10/2005	15/11/2005	SmPC and PL	Leflunomide, the active substance of Arava, was studied in a single multi-centre, randomised, double-blind, active-controlled trial in 94 patients (47 per arm) with polyarticular course Juvenile Rheumatoid Arthritis (JRA). Patients were 3-17 years of age with active polyarticular course JRA regardless of onset type and naive to methotrexate or leflunomide. In this trial, the loading dose and maintenance dose of leflunomide were based on three weight categories: children < 20 kg 100mg loading dose for 1 day followed by 10 mg every other day; children 20-40 kg: 100 mg loading dose for 2 days followed by 10 mg/day; children > 40 kg: 100 mg loading dose 3 days followed by 20 mg/day (the methotrexate dose was 0.5 mg/kg/week per os to a maximum of 25 mg/week). After 16 weeks treatment, the difference in response rates was statistically significant in favour of methotrexate for the JRA Definition of Improvement (DOI) = 30% (CI 95% : - 37.3 , -5.3; p=0.02) . This response was maintained during 48 weeks. The pattern of adverse events of leflunomide and methotrexate seems to be similar, but the dose used in lighter subjects resulted in a relatively low exposure (see below) which might have influenced safety data. These data do not allow an effective and safe dose

					recommendation in patients under 18 years. The pharmacokinetics of A771726, the active metabolite of leflunomide, following oral administration of leflunomide, have been investigated in 73 paediatric patients with polyarticular course JRA who ranged in age from 3 to 17 years. The results of a population pharmacokinetic analysis of these trials have demonstrated that paediatric patients with body weights = 40 kg have a reduced systemic exposure (measured by concentration at steady state) of A771726 relative to adult rheumatoid arthritis patients. Calculation via a pharmacokinetic model indicated that a leflunomide average steady state plasma concentration of about 34 µg/ml will be obtained in pediatr
II/0027	Update of section 4.8 "Undesirable effects" of the SPC to modify the frequency of severe infections including sepsis to rare, following the assessment of PSUR No. 10 and 11 (reporting period 12.03.2003-11.03.2004) and FUM20.3. The Package Leaflet was updated in accordance with the changes to the SPC. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	19/09/2005	SmPC and PL	The CHMP agreed that proposed changes to the SPC adequately reflect the current post-marketing cumulative experience with exposure to Arava and the available knowledge on severe infections including sepsis following the use of Arava. Considering the above safety update to the Product Information, the CHMP considered that the benefit/risk assessment of Arava remained favourable. The CHMP agreed with the proposed amendments of the PL.
II/0026	Update of sections 4.2 and 5.1 of the SPC following the CHMP assessment of study HWA 486/3012 on efficacy and safety of leflunomide 10 mg versus 20 mg daily doses in patients with active rheumatoid	21/10/2004	06/12/2004	SmPC and PL	The CHMP agreed that the proposed wording of sections 4.2 and 5.2 of the SPC adequately reflect the data from the randomised, double-blind, parallel-group comparative trial of the efficacy and safety of leflunomide 10mg versus 20mg

	arthritis. Update of Summary of Product Characteristics and Package Leaflet				daily doses in patients with active rheumatoid. The efficacy results of the 20 mg maintenance dose were more favourable, on the other hand, the safety results favoured the 10 mg daily maintenance dose. The recommended maintenance dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily. Patients may be started on leflunomide 10 mg or 20 mg depending on the severity (activity) of the disease. The CHMP agreed with the proposed amendments of the PL.
R/0024	Renewal of the marketing authorisation.	29/07/2004	13/10/2004	SmPC, Annex II, Labelling and PL	
II/0023	Update of SPC sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) to include a warning on interstitial pneumonia and to update the stated frequency for interstitial lung disease to "rare". Sections 2 and 4 of the Package Leaflet (PL) are amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	10/06/2004	SmPC and PL	
II/0022	Update of the Summary of Product Characteristics sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.3 (Contraindications) and 5.1 (Pharmacodynamic properties) to extend the indication to psoriatic arthritis and include results from a multinational randomised, double-blind placebo controlled study in patients with psoriatic arthritis.	24/03/2004	08/06/2004	SmPC and PL	

	The Package Leaflet has been amended accordingly. In addition, the MAH took the opportunity to update the adresses of Aventis EU affiliates and to add the list of local representatives for the 10 accession countries in section 6 of the Package Leaflet in accordance with EMEA/QRD templates. Extension of Indication				
IA/0025	IA_05_Change in the name and/or address of a manufacturer of the finished product	19/04/2004	n/a	Annex II and PL	
II/0021	Update of Summary of Product Characteristics	22/10/2003	27/01/2004	SmPC	
II/0020	to amend sections 4.2, 4.4 and 4.8 of the SPC based on PSUR 8 evaluation. The frequency of LFT monitoring has been increased to the same frequency as the complete blood cell count. Additional side-effects related to nervous, and haemic and lymphatic systems have been added. The PL is modified accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/07/2003	20/10/2003	SmPC and PL	
I/0019	Qualitative change to the primary packaging. 08_Change in the qualitative composition of immediate packaging material	16/01/2003	14/02/2003	SmPC	
II/0018	Update of Summary of Product Characteristics and Package Leaflet	25/04/2002	18/07/2002	SmPC and PL	

I/0017	20_Extension of shelf-life as foreseen at time of authorisation	15/01/2002	22/03/2002	SmPC	
I/0016	26_Changes to comply with supplements to pharmacopoeias	14/01/2002	06/03/2002		
I/0015	04_Replacement of an excipient with a comparable excipient	14/01/2002	06/03/2002		
I/0013	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	19/11/2001	19/02/2002	Annex II and PL	
I/0012	30_Change in pack size for a medicinal product	02/10/2001	19/02/2002	SmPC, Labelling and PL	
I/0014	11a_Change in the name of a manufacturer of the active substance	05/12/2001	07/01/2002		
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/09/2001	27/11/2001	PL	
II/0010	Update of Summary of Product Characteristics and Package Leaflet	29/03/2001	31/07/2001	SmPC and PL	
I/0009	26_Changes to comply with supplements to pharmacopoeias	02/04/2001	02/05/2001		
I/0006	03_Change in the name and/or address of the marketing authorisation holder 01_Change in the name of a manufacturer of the	25/08/2000	n/a	SmPC, Annex II, Labelling and PL	

	medicinal product 11a_Change in the name of a manufacturer of the active substance				
I/0005	12_Minor change of manufacturing process of the active substance	19/07/2000	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/05/2000	04/07/2000	PL	
I/0003	12_Minor change of manufacturing process of the active substance	03/05/2000	n/a		
II/0002	New safety warning	18/11/1999	24/03/2000	SmPC and PL	
I/0001	01_Change following modification(s) of the manufacturing authorisation(s)	20/09/1999	08/12/1999	Annex II and PL	