Leflunomide Zentiva

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
PSUSA/1837/ 202309	Periodic Safety Update EU Single assessment - leflunomide	30/05/2024	24/07/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1837/202309.
IB/0041/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any	21/06/2024		Annex II and PL	

[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).

	manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation 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) B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0040/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	18/04/2024	n/a		

	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 intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0038	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/01/2024	n/a		
IB/0037	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	13/05/2022	05/05/2023	SmPC, Labelling and PL	
IAIN/0036	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	20/07/2021	18/03/2022	Annex II and PL	
PSUSA/1837/ 202009	Periodic Safety Update EU Single assessment - leflunomide	06/05/2021	n/a		PRAC Recommendation - maintenance
IB/0035	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	08/03/2021	18/03/2022	SmPC, Annex II, Labelling and PL	

T/0032	Transfer of Marketing Authorisation	21/09/2018	16/10/2018	SmPC, Labelling and PL	
IAIN/0031	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	24/08/2018	16/10/2018	SmPC, Annex II, Labelling and PL	
PSUSA/1837/201709	Periodic Safety Update EU Single assessment - leflunomide	12/04/2018	n/a		PRAC Recommendation - maintenance
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2018	25/06/2018	Labelling and PL	
IG/0823	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/07/2017	25/06/2018	SmPC and PL	
PSUSA/1837/201609	Periodic Safety Update EU Single assessment - leflunomide	06/04/2017	n/a		PRAC Recommendation - maintenance
IA/0026	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/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/05/2016	14/10/2016	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	14/10/2016	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	14/10/2016	SmPC, Annex II and PL	
PSUSA/1837/ 201409	Periodic Safety Update EU Single assessment - leflunomide	10/04/2015	n/a		PRAC Recommendation - maintenance
R/0018	Renewal of the marketing authorisation.	25/09/2014	19/11/2014	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of leflunomide winthrop continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Leflunomide winthrop continues to be favourable in the treatment of active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD), and active psoriatic arthritis. The CHMP recommended the renewal of the Marketing Authorisation with unlimited validity.
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	19/11/2014	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	19/11/2014	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/0016	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	19/11/2014	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	20/12/2012	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/0011/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/0006	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	
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 or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.f - Changes to an existing pharmacovigilance	29/02/2012	n/a		

	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/0005	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	27/10/2011	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/0003	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 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/06/2011	27/07/2011	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 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/0004	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 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	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.

IB/0002	To update section 4.4 of the SmPC with information on PML. Minor editorial changes have also been made to section 2 of the SmPC, the labelling and the package leaflet. The MAH has also taken the opportunity to correct the contact details of the Slovak Republic local representative. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/05/2010	n/a	SmPC and PL	
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	