AUBAGIO

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/0048	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	17/09/2024		SmPC	
IB/0047	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	10/09/2024	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).

PSUSA/10135 /202309	Periodic Safety Update EU Single assessment - teriflunomide	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/10135/202309.
IB/0046	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/04/2024	24/07/2024	SmPC, Annex II and PL	
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2023	24/07/2024	PL	
IA/0043	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/05/2023	n/a		
II/0042	Submission of the final report of the open-label extension period for study EFC11759, listed as a category 3 study in the RMP. This is a two-year, multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate efficacy, safety, tolerability and pharmacokinetics of teriflunomide administered orally once daily in pediatric patients with relapsing forms of multiple sclerosis (MS) followed by an open-label extension. The RMP version 8.1 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/04/2023	n/a		
T/0040	Transfer of Marketing Authorisation	31/10/2022	21/11/2022	SmPC, Labelling and	

				PL	
IA/0041/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 intermediate used in the manufacture of the AS or manufacturer of a novel excipient	24/10/2022	n/a		
II/0038	Submission of the final PASS OBS12753 study report listed as a category 3 study in the RMP. This is a prospective cohort study of long-term safety of teriflunomide in multiple sclerosis patients in Europe. The updated RMP v 7.3 is agreed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/01/2022	n/a		
N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/11/2021	08/07/2022	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	08/07/2022	Annex II and PL	

PSUSA/10135 /202009	Periodic Safety Update EU Single assessment - teriflunomide	20/05/2021	23/07/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10135/202009.
X/0031/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/04/2021	17/06/2021	SmPC, Annex II, Labelling and PL	
IB/0036	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/02/2021	n/a		
II/0032	C.I.4. Update of section 4.4 of the SmPC in order to update information on the liver monitoring schedule and the use of concomitant potentially hepatotoxic drugs based on evidence from diverse clinical and postmarketing sources including results from three studies, namely TENERE/EFC10891 (Phase 3 multi-center, randomized, double-blind, open-label (for IFN β -1a), parallel-group study), Teri-PRO/LPS13567 study (Phase 4, multicenter, prospective, single-arm, open-label study) and TERIKIDS/EFC11759 (Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with 10 to 17 years of age), together with postmarketing data including real-world data from two European National Disease registries (The Danish Multiple Sclerosis Registry and Belgian Treatment in Multiple Sclerosis,	21/01/2021	17/06/2021	SmPC	Section 4.4 of the SmPC has been updated to inform about an update in liver monitoring. Liver enzimes should be assessed at least four weeks during the first 6 months and regularly thereafter. For patients with pre-existing liver disorders, concomitant use of potentially hepatotoxic drugs or those with signs or simtomps of liver injury, monitoring is recommended every two weeks during first 6 months and every 8 weeks thereafter for at least the first two years of treatment. In case of treatment discontinuation, liver tests should be pursued until normalisation of transaminase levels. For more information, reference is made to the Summary of Product Characteristics. Regarding further changes of the PI reference is made also to variation AUBAGIO EMEA/H/C/002514/II/0029.

	or BELTRIMS registry) and one US-based database of electronic health records (Optum Humedica Database) and postmarketing experience included in the Sanofi Global pharmacovigilance database. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0029	To update section 4.4 of the SmPC to add information on cases of drug-induced liver injury (DILI) observed in the postmarketing setting and section 4.8 of the SmPC to add of the adverse event DILI under the frequency unknown. During the assessment, it is considered that section 5.1 of the SmPC needs to be updated to reflect new information on pharmacological effects of teriflunomide based on newly reported proprietary data and scientific literature. The package leaflet is updated accordingly. In addition, the MAH took the opportunity to updated the PL local representatives details. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/01/2021	17/06/2021	SmPC and PL	Section 4.4 has been updated to reflect new information on drug-induced liver injury (DILI). Most cases of DILI ocurred several weeks or months after the initiation of the treatment with teriflunomide. Patients with pre-exisiting liver disorders, concomitant use of hepatotoxic drugs and or a substantial alcohol consumption have a higher risk of DILI. In case of elevated liver enzymes (>3ULN) or liver injury is supected, teriflunomide theraphy should be discontinued and accelerated elimination procedure should be also considered in the case of liver injury suspected. Section 4.8 has also been updated to include DILI as ADR with a frequency unknown. Section 5.1 has been updated to reflect new information on pharmacological effects of teriflunomide based on newly reported proprietary and literature. Regarding further changes of the PI reference is made also to variation AUBAGIO EMEA/H/C/002514/II/0032. For more information, please refer to the Summary of Product Characteristics.
II/0033	To update sections 4.4 and 4.8 of the SmPC regarding skin reactions in particular to drug reaction with eosinophilia and systemic symptoms (DRESS)	14/01/2021	17/06/2021	SmPC and PL	

	and to update the frequency of severe skin reactions from "Not known" to "Uncommon", following a review of the Sanofi global PV database. The Package Leaflet section 4 is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0034	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/12/2020	n/a		
II/0028	Submission of information in relation to human experience of use of teriflunomide during pregnancy from an analysis of the data recorded in the global safety database and available sources (clinical trial cases, registries and cohort studies, literature and post-marketing pregnancy reports). The MAH updated section 2 and 4.4 of the SmPC to align with the updated annex of the guideline excipients with regards to sodium. The Labelling and Package Leaflet are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/09/2020	18/11/2020	SmPC, Labelling and PL	Not applicable
IA/0030	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	26/03/2020	n/a		

II/0025	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/01/2020	18/11/2020	Annex II	
IB/0026/G	This was an application for a group of variations. 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.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	19/12/2019	18/11/2020	Annex II and PL	
IAIN/0027	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2019	18/11/2020	SmPC and PL	

IB/0024	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/05/2019	05/12/2019	SmPC and PL	
II/0022	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/04/2019	n/a		
II/0020	Submission of the final report from study LTS 6050. This is a phase 3 long term interventional study to document the safety of two doses of teriflunomide (7 and 14 mg) in patients with multiple sclerosis with relapses. Section 4.8 is updated to amend the frequency of nail disorder from unknown to uncommon and asthenia from unknown to common. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/02/2019	05/12/2019	SmPC and PL	The SmPC section 4.8 has been updated as follows: To update the frequency of nail disorder from unknown to uncommon and asthenia from unknown to common. The PL has been updated accordingly.
IAIN/0021	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/12/2018	05/12/2019	SmPC and PL	
IA/0019/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 B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation	03/08/2018	n/a		

IA/0018	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	28/06/2018	n/a		
R/0016	Renewal of the marketing authorisation.	22/03/2018	28/05/2018	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of AUBAGIO in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10135 /201709	Periodic Safety Update EU Single assessment - teriflunomide	12/04/2018	n/a		PRAC Recommendation - maintenance
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/10/2017	28/05/2018	PL	
IB/0013	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/07/2017	n/a		
IB/0014	A.z - Administrative change - Other variation	20/07/2017	n/a		
PSUSA/10135 /201609	Periodic Safety Update EU Single assessment - teriflunomide	21/04/2017	15/06/2017	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10135/201609.
IAIN/0012	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/06/2017	28/05/2018	SmPC, Annex II and PL	
IA/0010	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	02/12/2016	n/a		

	of the AS				
PSUSA/10135 /201503	Periodic Safety Update EU Single assessment - teriflunomide	22/10/2015	16/12/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10135/201503.
IB/0009/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	16/10/2015	n/a		
PSUSA/10135 /201409	Periodic Safety Update EU Single assessment - teriflunomide	23/04/2015	19/06/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10135/201409.
PSUV/0005	Periodic Safety Update	25/09/2014	19/11/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0005.
II/0003	Update of sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) following the completion of study TOPIC. The patient leaflet is updated accordingly. In addition, section 4.5 was updated to improve the wording related to the oral	25/09/2014	19/11/2014	SmPC and PL	After the review of the data, the CHMP recommended the update of the summary of the safety profile of the product including updated frequencies of existing adverse drug reactions (ADRs) and addition of new ADRs (upper abdominal pain). In addition, the following information was

	contraceptive pharmacokinetics interaction. Minor editorial changes are introduced throughout the Product Information (PI). Additionally, the MAH took the opportunity to update the list of local representatives in the Package Leaflet (PL). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				included in section 5.1 of the SmPC: The TOPIC was a double-blind, placebo-controlled study that evaluated once daily doses of teriflunomide 7 mg and 14 mg for up to 108 weeks in patients with first clinical demyelinating event (mean age 32.1 years). The primary endpoint was time to a second clinical episode (relapse). A total of 618 patients were randomized to receive 7 mg (n=205) or 14 mg (n=216) of teriflunomide or placebo (n=197). The risk of a second clinical attack over 2 two years was 35.9% in the placebo group and 24.0% in the teriflunomide 14 mg treatment group (hazard ratio: 0.57, 95% confidence interval: 0.38 to 0.87, p=0.0087). The results from the TOPIC study confirmed the efficacy of teriflunomide in RRMS (including early RRMS with first clinical demyelinating event and MRI lesions disseminated in time and space).
II/0004	Update of the section 4.4 with results of the second vaccination study, PDY12738 performed with vaccinations to inactivated neoantigen. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	19/11/2014	SmPC	In this variation the company added the information from two clinical studies which have shown that both the first vaccination and re-exposure to inactivated vaccine are safe and effective during treatment with AUBAGIO; however, the use of live (attenuated) vaccines should be avoided.
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		
IAIN/0002	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the	19/12/2013	19/11/2014	SmPC and PL	

	list of medicinal products that are subject to additional monitoring				
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/12/2013	19/11/2014	PL	