Hetlioz

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
IAIN/0032/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	10/10/2022		SmPC, Annex II, Labelling 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).

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IB/0030	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	31/08/2022		SmPC	
IB/0029	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	14/03/2022	n/a		
PSUSA/10394 /202107	Periodic Safety Update EU Single assessment - tasimelteon	10/02/2022	n/a		PRAC Recommendation - maintenance
IA/0027	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	04/10/2021	n/a		
PSUSA/10394 /202101	Periodic Safety Update EU Single assessment - tasimelteon	02/09/2021	n/a		PRAC Recommendation - maintenance
IAIN/0026	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	11/06/2021	01/07/2022	SmPC, Annex II and PL	

IAIN/0025	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	22/04/2021	n/a		
IA/0023/G	This was an application for a group of variations. B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	25/02/2021	n/a		
IAIN/0022	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/02/2021	n/a		
PSUSA/10394 /202007	Periodic Safety Update EU Single assessment - tasimelteon	11/02/2021	n/a		PRAC Recommendation - maintenance
T/0020	Transfer of Marketing Authorisation	13/08/2020	17/09/2020	SmPC, Labelling and PL	
PSUSA/10394 /202001	Periodic Safety Update EU Single assessment - tasimelteon	03/09/2020	n/a		PRAC Recommendation - maintenance

R/0018	Renewal of the marketing authorisation.	30/04/2020	03/07/2020	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Hetlioz in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10394 /201907	Periodic Safety Update EU Single assessment - tasimelteon	16/01/2020	n/a		PRAC Recommendation - maintenance
PSUSA/10394 /201901	Periodic Safety Update EU Single assessment - tasimelteon	11/07/2019	n/a		PRAC Recommendation - maintenance
IAIN/0016/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	01/04/2019	n/a		
IAIN/0014/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	29/03/2019	28/02/2020	Annex II and PL	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
T/0013	Transfer of Marketing Authorisation	19/12/2018	25/02/2019	SmPC, Labelling and PL	
PSUSA/10394 /201807	Periodic Safety Update EU Single assessment - tasimelteon	17/01/2019	n/a		PRAC Recommendation - maintenance
PSUSA/10394 /201801	Periodic Safety Update EU Single assessment - tasimelteon	12/07/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10394 /201707	Periodic Safety Update EU Single assessment - tasimelteon	11/01/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10394 /201701	Periodic Safety Update EU Single assessment - tasimelteon	06/07/2017	n/a		PRAC Recommendation - maintenance
II/0008	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/07/2017	01/12/2017	SmPC	Data presented showed that the concomitant administration of tasimelteon with inducers or inhibitors of CYP2C19 is not expected to alter plasma concentrations or exposure of tasimelteon or its metabolites in a clinically meaningful way. Therefore a healthy volunteer study to investigate the CYP2C19 Drug-Drug Interaction potential is not needed. Caution should be used when administering Hetlioz in combination with fluvoxamine or other strong CYP1A2 inhibitors, particularly those which also inhibit other enzymes involved in the clearance of Hetlioz because of a potentially large increase in tasimelteon exposure and

					greater risk of adverse reactions. CYP1A2 and CYP3A4 are enzymes identified to play a role in the metabolism of tasimelteon, with a minor role for CYP2C9/C19. Medicinal products that inhibit CYP1A2 and CYP3A4 have been shown to alter the metabolism of tasimelteon in vivo. Caution should be used when administering tasimelteon in combination with fluvoxamine or other strong CYP1A2 inhibitors such as ciprofloxacin and enoxacin because of a potentially large increase in tasimelteon exposure and greater risk of adverse reactions: the AUC0-inf and Cmax of tasimelteon increased by 7-fold and 2-fold, respectively, when co-administered with fluvoxamine 50 mg (after 6 days of fluvoxamine 50 mg per day). This is deemed even more important for strong CYP1A2 inhibitors also inhibiting other enzymes involved in the clearance of HETLIOZ (e.g. fluvoxamine and ciprofloxacin). Tasimelteon is extensively metabolised. Metabolism of tasimelteon consists primarily of oxidation at multiple sites and oxidative dealkylation resulting in opening of the dihydrofuran ring followed by further oxidation to give a carboxylic acid. CYP1A2 (35.4%) and CYP3A4 (24.3%) are the major enzymes identified to play a role in the metabolism of tasimelteon. CYP2C9 (18.8%) and CYP2C19 (15.1%) also contribute to the metabolism of tasimelteon. Tasimelteon clearance does not appear to be affected by polymorphisms in these enzymes.
II/0007	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/03/2017	n/a		In order to address concerns regarding the phototoxicity potential of tasimelteon and its main metabolites, the Marketing Authorisation Holder (MAH) has submitted three in vitro studies in fulfilment of post authorisation measure

					MEA 004. First, the MAH conducted a study to determine the molar extinction coefficient for tasimelteon and its main metabolites (Study VCR-TMI-121012). Molar extinction coefficient (MEC) values for metabolites M3, M12, and M13 were above 1000 L/mol/cm. Therefore, further testing was undertaken with these metabolites in an in vitro phototoxicity test as recommended by the ICH Guideline S10. Subsequently two studies were conducted to assess the phototoxicity potential of tasimelteon's metabolites M12, M14, and M3 (TAJ0044 and TAJ0045). The results of the in vitro tests indicated that metabolites M3, M12 and M14 do not show phototoxic potential in the UVA range of 315 – 380 nm. However, the findings were limited to the UVA range as the metabolites absorb at approximately 290 nm which is below the threshold of compounds that warrant phototoxicity testing, metabolites (in-line with ICH Guidance S10) generally do not warrant separate photosafety assessments, as metabolism does not typically result in chromophores that are substantially different from those in the parent molecule and there have been no phototoxic signals seen in patients in the post-marketing data collected so far. No further phototoxicity testing is required.
PSUSA/10394 /201607	Periodic Safety Update EU Single assessment - tasimelteon	12/01/2017	n/a		PRAC Recommendation - maintenance
IAIN/0006	A.1 - Administrative change - Change in the name and/or address of the MAH	21/12/2016	01/12/2017	SmPC, Labelling and PL	
PSUSA/10394	Periodic Safety Update EU Single assessment -	02/09/2016	n/a		PRAC Recommendation - maintenance

/201601	tasimelteon				
II/0003/G	This was an application for a group of variations. Submission of: -In vitro pharmacokinetic study XT154077-category 3 study in the RMP in order to fulfil MEA 009. -In vitro pharmacokinetic study XT154076 -category 3 study in the RMP in order to fulfil MEA 010. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/05/2016	n/a		
II/0002	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	19/11/2015	n/a		
II/0001	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	19/11/2015	n/a		