Orfadin

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
IB/0082	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)	13/04/2023		SmPC	
IB/0081	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	04/01/2023	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).

	material/intermediate/reagent - Other variation				
IB/0080	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/11/2022	n/a		
PSUSA/2169/202202	Periodic Safety Update EU Single assessment - nitisinone	29/09/2022	n/a		PRAC Recommendation - maintenance
IA/0078/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer 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 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.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	18/02/2022	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
PSUSA/2169/ 202102	Periodic Safety Update EU Single assessment - nitisinone	30/09/2021	n/a		PRAC Recommendation - maintenance
IA/0077	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	25/08/2021	n/a		
II/0075	B.II.b.5.d - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of an in-process test which may have a significant effect on the overall quality of the finished product	28/05/2021	n/a		
II/0074	Submission of the final report from study Sobi.NTBC-005 listed as a category 3 study in the RMP. This is a non-interventional Post Authorization Safety Study (PASS) to evaluate long-term safety of Orfadin treatment in hypertyrosinemia type 1 (HT-1) patients in standard clinical care. The RMP version 5.5 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	11/02/2021	n/a		
II/0071	Extension of indication to include treatment of adult	17/09/2020	22/10/2020	SmPC and PL	Please refer to Scientific Discussion ‘Orfadin-H-C-000555-

	patients with alkaptonuria (AKU) for Orfadin; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 10 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.2 of the RMP has also been submitted accordingly and includes an update in accordance with GVP Module V Revision 2. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				II-71’
PSUSA/2169/ 202002	Periodic Safety Update EU Single assessment - nitisinone	01/10/2020	n/a		PRAC Recommendation - maintenance
IA/0072/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates	08/05/2020	n/a		

	exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IAIN/0070	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	20/12/2019	22/10/2020	Annex II and PL	
PSUSA/2169/ 201902	Periodic Safety Update EU Single assessment - nitisinone	05/09/2019	n/a		PRAC Recommendation - maintenance
IAIN/0068/G	This was an application for a group of variations. B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is	02/04/2019	n/a		

	not an integrated part of the primary packaging - Device with CE marking				
II/0067	Update of sections 4.4, 4.5 and 5.2 to add a warning on interaction with medicinal products with a narrow therapeutic window metabolized through CYP2C9 and information based on in vitro and in vivo drug drug interaction studies investigating effects of nitisinone on cytochromes CYP2C9,CYP2D6, CYP2E1, OAT1, OAT3, CYP2D6, CYP1A2, CYP2B6, CYP3A4/5, P-gp, BCRP, OATP1B1, OATP1B3 or OCT2-mediated transport. This update is following PRAC conclusions on PSUSA (EMEA/H/C/PSUSA/00002169/201802) adopted on 6 September 2018. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	07/03/2019	05/12/2019	SmPC and PL	New information on in vivo and in vitro interactions were added to the Product Information. This included a warning that nitisinone, as a moderate inhibitor of CYP2C9, may result in increased plasma concentrations of co-administered medicinal products metabolized primarily via CYP2C9. Nitisinone treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolized through CYP2C9, such as warfarin and phenytoin, should be monitored for toxicity of the co-administered medicinal products.
IB/0066/G	This was an application for a group of variations. 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) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	19/12/2018	05/12/2019	SmPC, Labelling and PL	
PSUSA/2169/201802	Periodic Safety Update EU Single assessment - nitisinone	20/09/2018	20/11/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2169/201802.

IA/0065/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished 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.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms 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 B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	13/07/2018	n/a		

	Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0063	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	16/10/2017	n/a		
PSUSA/2169/ 201702	Periodic Safety Update EU Single assessment - nitisinone	28/09/2017	n/a		PRAC Recommendation - maintenance
IA/0061	B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method	24/04/2017	n/a		
IA/0060/G	This was an application for a group of variations. 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 B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS -	17/03/2017	n/a		

	Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0057	Update of sections 4.2 and 5.1 of the SmPC in order to amend the dosing frequency further to the results of a clinical pharmacology study NTBC-003. The Package Leaflet and Risk Management Plan are updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	26/01/2017	SmPC and PL	In view of results from a clinical pharmacology study, the Product Information was updated with regards to the dosing frequency. The following revisions were introduced in section 3 of the Package Leaflet (How to take Orfadin) to update the information on dosing (new text bold, old text in strikethrough mode): The recommended total daily dose is 1 mg/ kg body weight taken once daily divided in 2 doses administered orally. Your doctor will adjust the dose individually. It is recommended to administer the dose once daily, administered orally. However, due to the limited data in patients with body weight <20 kg, it is recommended to

					divide the total daily dose into two daily administrations in this patient population.
II/0056	Update of section 5.1 of the SmPC in order to present the efficacy data based on a complementary analysis of the pivotal study for Orfadin (NTBC study). In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the Product Information in line with the latest QRD template version 10. The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	26/01/2017	SmPC, Annex II, Labelling and PL	In view of a complementary analysis of the pivotal NTBC study as well as data from a study used as a historical control (van Spronsen et al., 1994) the tables presenting survival probabilities were updated in section 5.1 of the SmPC. In addition, further details on the reduction of risk of development of hepatocellular carcinoma were included in a tabular format in section 5.1 of the SmPC.
IA/0059/G	This was an application for a group of variations. 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	22/11/2016	n/a		
II/0058	Update of section 5.3 of the SmPC in order to add a statement that carcinogenic potential was not shown in a 26-week carcinogenicity study	15/09/2016	26/01/2017	SmPC	The following change to the SmPC Section 5.3 is introduced with this variation: Nitisinone did not show carcinogenic potential in a 26-week

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				carcinogenicity study in transgenic mice (TgrasH2).
PSUSA/2169/ 201602	Periodic Safety Update EU Single assessment - nitisinone	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0055	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	09/06/2016	n/a		
IA/0053	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	25/05/2016	n/a		
IA/0052	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	04/02/2016	n/a		
IB/0051	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	05/01/2016	n/a		
IA/0050/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	16/11/2015	n/a		

	B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
IB/0049	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	26/10/2015	n/a		
IA/0048	B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	21/10/2015	n/a		
PSUSA/2169/ 201502	Periodic Safety Update EU Single assessment - nitisinone	10/09/2015	n/a		PRAC Recommendation - maintenance
X/0041	To add a new pharmaceutical form: oral suspension Annex I_2.(d) Change or addition of a new pharmaceutical form	23/04/2015	19/06/2015	SmPC, Annex II, Labelling and PL	
X/0042	To add a new strength 20 mg capsule, hard. Annex I_2.(c) Change or addition of a new strength/potency	26/02/2015	05/05/2015	SmPC, Labelling and PL	
IA/0046	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/11/2014	n/a		

PSUV/0044	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IB/0045	To reduce in-use storage time of the finished product from "a single period of 3 months" to " a single period of 2 months" at a temperature not above 25°C. B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	25/07/2014	05/05/2015	SmPC, Labelling and PL	
IAIN/0043	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	08/04/2014	n/a		
IB/0039	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	25/09/2013	n/a		
IAIN/0040	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	19/07/2013	27/06/2014	SmPC and PL	
IA/0038	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/12/2012	n/a		
IA/0037	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	15/10/2012	n/a		

	procedure				
IA/0036	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	10/10/2012	n/a		
IB/0034	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	23/07/2012	n/a		
IB/0031	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	02/03/2012	n/a		
IA/0033/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	27/02/2012	n/a		
IA/0032	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	31/01/2012	n/a		
IA/0030	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	30/11/2011	n/a		

IB/0029	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	15/06/2011	n/a		
IB/0028	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	15/06/2011	n/a		
IA/0027/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	28/02/2011	n/a		
IA/0026/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding	26/10/2010	n/a	SmPC, Annex II, Labelling and PL	

	manufacturer for batch release)				
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/07/2010	n/a	PL	
R/0021	Renewal of the marketing authorisation.	19/11/2009	19/01/2010	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 was of the opinion that the quality, safety and efficacy of Orfadin continue to be adequately and sufficiently demonstrated. Orfadin remains the only therapeutic treatment so far available for the treatment of the rare disease tyrosinemia type 1 and the risk/benefit of Orfadin in the treatment of the approved indication continues to be favourable. The CHMP was of the opinion that the renewal could be granted with unlimited validity.
IA/0022	IA_13_a_Change in test proc. for active substance - minor change	11/01/2010	n/a		
S/0019	ANNUAL REASSESSMENT	25/06/2009	21/09/2009	SmPC, Annex II and PL	"The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable. The CHMP considered that, as all specific obligations have been fulfilled, there are no remaining grounds for the Marketing Authorisations to remain under exceptional circumstances."
IA/0020	IA_05_Change in the name and/or address of a	27/07/2009	n/a	Annex II and	

	manufacturer of the finished product			PL	
IA/0018	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	14/10/2008	n/a		
IA/0017	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	14/10/2008	n/a		
IA/0016	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	14/10/2008	n/a		
IA/0015	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	14/10/2008	n/a		
S/0014	Annual re-assessment.	26/06/2008	n/a		The CHMP having reviewed the evidence of compliance with the Specific Obligations submitted by the MAH and having re-assessed the benefit/risk profile of Orfadin, considered that no update of the Community Marketing Authorisation was necessary. The overall benefit/risk of Orfadin in the treatment of the approved indication remains unchanged. The CHMP agreed that the Marketing Authorisation should be kept under exceptional circumstances.
IB/0013	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	29/04/2008	n/a		
IB/0012	IB_10_Minor change in the manufacturing process of the active substance	29/04/2008	n/a		

IB/0011	IB_17_a_Change in re-test period of the active substance	29/04/2008	n/a		
IB/0010	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	29/04/2008	n/a		
IA/0009	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	19/02/2008	n/a		
S/0008	Annual re-assessment.	21/06/2007	23/08/2007	Annex II	The CHMP having reviewed the evidence of compliance with the Specific Obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of Orfadin, concluded that, overall, the benefit/risk ratio for the medicinal product remains unchanged. The CHMP also considered that the Specific Obligation to further analyse the remaining histological samples from the 12 and 6 month rodent toxicity studies can be considered fulfilled based on the final study report submitted in June 2006. The CHMP considered that the Marketing Authorisation should be kept under exceptional circumstances and agreed on a revised list of Specific Obligations.
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2007	n/a	PL	
IA/0006	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	24/11/2006	n/a		

S/0003	Annual re-assessment.	28/06/2006	28/08/2006	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the evidence of compliance with the Specific Obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of Orfadin, concluded that, overall, the benefit/risk ratio for the medicinal product remains unchanged. The CHMP considered that the marketing authorisation should be kept under exceptional circumstances, and agreed on a revised list of Specific Obligations.
IA/0005	IA_39_Change/addition of imprints, bossing or other markings	07/06/2006	n/a	SmPC and PL	
IA/0004	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	07/06/2006	n/a		
II/0002	Update of section 4.4 of the Summary of Product Characteristics to include a warning recommending monitoring visits every 6 months or shorter intervals in case of AEs. Update of Summary of Product Characteristics	23/03/2006	18/04/2006	SmPC	Following the evaluation of the Post Marketing Surveillance (PMS) programme to monitor hepatic, renal, haematological, neurological and ophthalmic status on all patients treated with the product, the CHMP was of the opinion that the follow-up visits should take place at shorter intervals. Therefore, the CHMP requested to the MAH to include a warning in section 4.4 of the SPC recommending monitoring visits every 6 months or shorter intervals in case of AEs. The MAH submitted this type II variation to update the SPC as requested by the CHMP.
IA/0001	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	08/09/2005	n/a		