Cufence

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
II/0020	Update of section 4.2 of the SmPC, Annex II and the RMP based on the submission of the PK/PD sub-study report for study UNV-TR-004 (UNITED) listed as a PAES in the Annex II of the Product Information. This is an open label, prospective study to characterize the pharmacokinetics and pharmacodynamics of Cufence and to investigate the efficacy and safety in Wilson's disease. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	08/05/2025	25/06/2025	SmPC and Annex II	The results of the PK/PD sub-study report indicated comparably high post-dose trientine concentrations in patients with predominantly neurologic symptoms. Whilst the dataset is limited and final conclusions can only be made upon availability of the main study when all pharmacokinetic samples collected over the course of the 24 months are available it was added in the posology statement that in patients primarily presenting neurological symptoms up titration can be initiated at the minimum available dose. For more information, please refer to the Summary of Product Characteristics.

[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).

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
R/0016	Renewal of the marketing authorisation.	21/03/2024	16/05/2024	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 Cufence in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. The product information was updated with the latest QRD template.
IB/0018	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/04/2024	25/04/2025	Annex II	
PSUSA/10637 /202309	Periodic Safety Update EU Single assessment - trientine	11/04/2024	n/a		PRAC Recommendation - maintenance
IA/0019	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	15/03/2024	n/a		
X/0014/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	14/09/2023	23/11/2023	SmPC, Annex II, Labelling and PL	
IA/0015	B.I.b.2.a - Change in test procedure for AS or	27/03/2023	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0013/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.7 - Administrative change - Deletion of manufacturing sites	15/12/2022	n/a		
IA/0012	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/10/2022	n/a		
IB/0011	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	17/10/2022	23/11/2023	Annex II	To change the due date for the study reports for study UNV-TR-004 (Efficacy and safety of trientine dihydrochloride in Wilson's disease patients), as follows: - PK/PD sub-study report: from 'Q4, 2022' to 'Q4, 2023' - Main study report: from 'Q4, 2025' to 'Q4, 2026'.
PSUSA/10637 /202109	Periodic Safety Update EU Single assessment - trientine	07/04/2022	n/a		PRAC Recommendation - maintenance
IA/0010	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	28/02/2022	n/a		
IA/0008	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	26/07/2021	n/a		

	material/intermediate/reagent - Tightening of specification limits				
II/0007/G	This was an application for a group of variations. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	20/05/2021	02/06/2022	SmPC, Labelling and PL	The SmPC section 6.4 has been updated to change the storage conditions of the finished product after opening from 'store in a refrigerator (2ºC-8ºC), do not freeze' to 'no special storage conditions'. The Labelling and PL have been updated accordingly.
PSUSA/10637 /202009	Periodic Safety Update EU Single assessment - trientine	09/04/2021	n/a		PRAC Recommendation - maintenance
PSUSA/10637 /201909	Periodic Safety Update EU Single assessment - trientine	17/04/2020	n/a		PRAC Recommendation - maintenance
IAIN/0005/G	This was an application for a group of variations. B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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 B.II.f.1.e - Stability of FP - Change to an approved stability protocol	26/03/2020	n/a		

	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.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 exist per material)				
II/0002/G	This was an application for a group of variations. C.1.4. Update of sections updates of sections 4.5 and 5.2 of the SmPC in order to add information on food interaction and pk based on results from study TR-003 PK are proposed. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template. 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 B.II.a.3.b.2 - Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the product	30/01/2020	18/11/2020	SmPC, Labelling and PL	Study TR-003 PK was a single-dose, open label, randomized, three-way cross-over study in healthy volunteers to characterize the pharmacokinetics of the 300 mg trientine capsule and to assess the effect of dissolution rate and the effect of food on the pharmacokinetics of trientine. The data showed that trientinie is absorbed with tmax occurring between 0.5 and 6 hours post-dose and the variation between subjects is of up to 60%. The intake of food within 30 minutes prior to trientine administration delayed the time to peak concentrations by 2 hours and reduces the extent of absorption of trientine by approximately 45%. The data further indicated that the plasma exposure to the MAT metabolite is approximately 3 times that of unchanged trientine, while exposure to the DAT metabolite is slightly lower compared to trientine. The metabolites of trientine have Cu-chelating properties, however the stability of these Cu-complexes is low due to the introduction of the acetyl

	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.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				groups. The contribution of chelating activity by the MAT and DAT metabolites appeared to be limited. After absorption trientine and its metabolites are rapidly excreted in the urine, either bound to copper or unbound. The unabsorbed fraction of orally administered trientine is bound to intestinal copper and eliminated through faecal excretion. The elimination half-life of trientine is approximately 4 hours (mean t1/2 of 3.8 ± 1.3 hours measured at steady state in WD patients and 4.4 ± 4.7 hours measured after a single dose in healthy volunteers). The elimination half-lives of the two metabolites were 14.1 ± 3.7 hours for MAT and 8.5 ± 3.0 hours for DAT after a single dose administration of trientine in healthy subjects. The data from healthy subjects indicate that age, gender and body weight do not seem to influence the pharmacokinetics of trientine. Based on quality data the information on storage of the medicinal product was updated in the product information to reflect that no special storage condition is needed when unopened. After opening the bottle should be stored in a refrigerator (2ºC 8ºC).
IAIN/0003/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.3.a - 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 - Implementation of wording agreed by the competent authority	27/11/2019	18/11/2020	SmPC, Labelling and PL	

IAIN/0001/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.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	18/09/2019	n/a		