TEPADINA

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/0050/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	13/06/2024		SmPC, 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).

	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.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.z - Change in container closure system of the Finished Product - Other variation 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.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)				
X/0049	Annex I_2.(c) Change or addition of a new strength/potency	25/01/2024	21/03/2024	SmPC, Labelling and PL	
IB/0051/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.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale	29/02/2024		SmPC	

	(supported by real time data)				
IA/0048	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	12/06/2023	n/a		
II/0046/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.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	30/03/2023	n/a		
IB/0047	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	28/03/2023	21/03/2024	SmPC, Labelling and PL	
IB/0044	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)	05/01/2022	08/07/2022	SmPC and PL	To update the shelf life of Tepadina 400mg from '18 months' to '24 months' in section 6.3 of the Summary of Product Characteristics (SmPC). To update the list of local representatives in the package

					leaflets.
IB/0043/G	This was an application for a group of variations. 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 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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	09/12/2021	n/a		
PSUSA/2932/ 202103	Periodic Safety Update EU Single assessment - thiotepa	02/12/2021	n/a		PRAC Recommendation - maintenance
IB/0042/G	This was an application for a group of variations. 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.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.z - Change in the manufacturing process of the finished or intermediate product - Other variation	06/09/2021	n/a		

IB/0040	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)	05/08/2021	08/07/2022	SmPC, Labelling and PL	
X/0036	Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form	28/01/2021	26/03/2021	SmPC, Labelling and PL	
IB/0039/G	This was an application for a group of variations. 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 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 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.c.1.z - Change in immediate packaging of the AS - Other variation 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	20/11/2020	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IB/0038/G	This was an application for a group of variations. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - 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 A.7 - Administrative change - Deletion of manufacturing sites	03/11/2020	26/03/2021	SmPC, Annex II and PL	
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/01/2020	03/11/2020	PL	

II/0034	B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF	12/12/2019	n/a		
II/0035/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation 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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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 B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	14/11/2019	03/11/2020	SmPC, Annex II and PL	
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/06/2019	03/11/2020	PL	
IA/0032/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/12/2018	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/2932/201803	Periodic Safety Update EU Single assessment - thiotepa	31/10/2018	n/a		PRAC Recommendation - maintenance
IAIN/0030/G	This was an application for a group of variations. 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) 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.5.a - Change to in-process tests or limits	29/11/2017	02/08/2018	Annex II and PL	

	applied during the manufacture of the finished product - Tightening of in-process limits				
IB/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/08/2017	02/08/2018	SmPC, Annex II, Labelling and PL	
IA/0028/G	This was an application for a group of variations. 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.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	05/12/2016	n/a		
N/0027	Update of the package leaflet with revised contact details of the local representative for France. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/04/2016	12/05/2016	PL	
II/0026	Update of section 4.8 of the SmPC in order to update the safety information on leukoencephalopathy. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make editorial changes in the PI. C.I.3.b - 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 - Change(s) with	25/02/2016	12/05/2016	SmPC and PL	

	new additional data submitted by the MAH				
PSUSA/2932/ 201503	Periodic Safety Update EU Single assessment - thiotepa	06/11/2015	n/a		PRAC Recommendation - maintenance
II/0025/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.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products 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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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.a - Change in the batch size (including batch	05/11/2015	n/a		

	size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size 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.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 B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test 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.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products				
II/0021	Update of section 4.8 of the SmPC to add the ADR 'severe toxic skin reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis' with unknown frequency. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details for the local representatives in Greece and	24/09/2015	12/05/2016	SmPC and PL	N/A

	Cyprus in the Package Leaflet. A revised RMP version 12 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0023	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	16/07/2015	n/a		
IA/0022/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	06/07/2015	n/a		
II/0018	Update of section 4.8 of the SmPC in order to add pulmonary arterial hypertension as a new adverse drug reaction (ADR) with unknown frequency in the paediatric population. The Package Leaflet and the RMP (version 11.0) are updated accordingly. The MAH also took the opportunity to make some editorial changes according to the QRD template, to align the package leaflet between strengths and to update the local representative information for Croatia in the Package Leaflet. In addition, a minor change was introduced in the address of the	21/05/2015	12/05/2016	SmPC, Labelling and PL	Pulmonary Arterial hypertension is added as an adverse drug reaction to the Tepadina product information after analysis of worldwide post-marketing experience, clinical-trial data and literature.

	Marketing Authorisation Holder as agreed with the Agency. A revised RMP (version 11.0) is agreed including the new important potential risk of pulmonary arterial hypertension. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0019	B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue	11/04/2015	n/a		
IAIN/0020	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	16/03/2015	n/a		
R/0017	Renewal of the marketing authorisation.	25/09/2014	17/11/2014	SmPC, Labelling and PL	Based on the review of the available information, the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers the benefit/risk profile of Tepadina continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/06/2014	17/11/2014	PL	
IAIN/0015	B.II.b.1.a - Replacement or addition of a	19/05/2014	n/a		

	manufacturing site for the FP - Secondary packaging site				
IAIN/0014	Infertility is an adverse drug reaction of chemotherapeutic regimens employing Tepadina which occurs at a frequency 'common' (affects up to 1 to 10 people)'. 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	21/02/2014	28/04/2014	SmPC, Annex II, Labelling and PL	
IAIN/0013/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.7 - Administrative change - Deletion of manufacturing sites	18/10/2013	28/04/2014	SmPC, Labelling and PL	
IAIN/0012/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	05/08/2013	n/a		

	C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking 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/0010/G	This was an application for a group of variations. Change to the method and specification for the parameter clarity of solution. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	25/04/2013	25/04/2013	SmPC and PL	
IAIN/0011/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	15/04/2013	28/04/2014	Annex II and PL	
IAIN/0009/G	This was an application for a group of variations.	31/08/2012	n/a		

	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in 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.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				
IA/0008	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	01/06/2012	n/a		
N/0006	Update of the Greek local representative contact details and deletion of duplicate information in the Spanish package leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/01/2012	28/04/2014	PL	
II/0004/G	This was an application for a group of variations. This was an application for a group of variations. Update of sections 4.2 and 6.6 of the SmPC regarding reconstitution instructions and final target concentration in the solution for infusion and update of section 6.3 of the SmPC to amend shelf life. The PL was updated accordingly and additional changes were made to bring the PL in line with the SmPC.	21/07/2011	26/08/2011	SmPC, Annex II and PL	Each 15 mg Tepadina vial must be reconstituted with 1.5 ml of sterile water for injection (10 ml for each 100 mg vial). The total volume of reconstituted vials to be administered should be further diluted in 500 ml of sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration (1000 ml if the dose is higher than 500 mg). In children, if the dose is lower than 250 mg, an appropriate volume of sodium chloride 9 mg/ml (0.9%) solution for injection may be used in order to obtain a final

	The version number of the Pharmacovigilance System was deleted from Annex II, a mistake was corrected in section 4.2 of the SmPC and in the PL, the list of local representatives in the PL was updated and additional changes were made to the PI in accordance with the latest version of the QRD template (v 7.3.1 March 2010) C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)				TEPADINA concentration between 0.5 and 1 mg/ml. Chemical and physical in use stability of Tepadina after dilution has been demonstrated for 24 hours when stored at 2 8°C and for 4 hours when stored at 25°C.
IB/0005/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	03/05/2011	n/a		

	specification limits B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State				
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2011	n/a	PL	
IA/0001/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	21/05/2010	n/a	Annex II	