NexoBrid

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/0058	Extension of current indication for removal of eschar in adults with deep partial- and full-thickness thermal burns to the paediatric population for NexoBrid based on interim results from study MW2012-01-01 (CIDS study), listed as Study MW2012-01-01 is a 3-stage, multi-centre, multi-national, randomised, controlled,	09/11/2023	14/12/2023	SmPC and PL	Please refer to Scientific Discussion 'NexoBrid-H-C-002246-II-Var.0058'.

[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).

	open label, 2 arm study aiming to demonstrate the superiority of NexoBrid treatment over SOC treatment in paediatric patients (aged 0 to 18 years) with deep partial thickness (DPT) and full thickness (FT) thermal burns of 1% to 30% of total body surface area (TBSA). As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Annex II and Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to remove the black triangle from the SmPC and the package leaflet, combine the SmPCs and introduce minor editorial corrections to the product information. Version 9.4 of the RMP is acceptable. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0066	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	30/11/2023	n/a		
PSUSA/10028 /202212	Periodic Safety Update EU Single assessment - concentrate of proteolytic enzymes enriched in bromelain	31/08/2023	n/a		PRAC Recommendation - maintenance
IB/0065	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/08/2023	n/a		

IB/0064	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	28/04/2023	n/a		
II/0057	Submission of the 24-months' CSR addendum of the MW2010-03-02 (DETECT) category 1 study; a multicentre, multinational, randomized, controlled, assessor blinded study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to gel vehicle and compared to standard of care. The provision of the CSR addresses the post-authorisation measure ANX 001.7. The updated RMP version 8.2 was considered acceptable. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/03/2023	14/12/2023	SmPC and Annex II	SmPC section 5.1 is updated to include the 24 months results of study MW2010-03-02 (DETECT). Treatment with NexoBrid did not have clinically meaningful deleterious effect on burn scar cosmesis and function compared with the SOC treatment at 24 months after wound closure.
IA/0062	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	27/02/2023	n/a		
IA/0061/G	This was an application for a group of variations. B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	15/02/2023	n/a		

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
IAIN/0060	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	24/01/2023	14/12/2023	Annex II and PL	

R/0056	Renewal of the marketing authorisation.	23/06/2022	12/08/2022	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of NexoBrid in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0049	Update of sections 4.2, 4.4, 4.8, 5.1, 5.2, 6.2 and 6.6 of the SmPC based on literature references and on interim results from study MW2010-03-02 (DETECT) listed as an obligation in the Annex II; this is a multicenter, multinational, randomized, controlled, assessor blinded, three-arm study performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to Gel Vehicle and compared to Standard of Care. The submitted Clinical Study Report includes data of Acute Phase and 12 months Follow Up Period including sub-studies on PK parameters, immunogenicity and cardiac ECG testing. In addition, the MAH took the opportunity to revise the due date of the final study report for study MW2010-03-02 as agreed in procedure EMEA/H/C/002246/IB/0054. Furthermore, the PI is brought in line with the latest QRD template version 10.2. The Package Leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/11/2021	21/06/2022	SmPC and PL	Based on interim results from study MW2010-03-02 (DETECT) and on literature references, SmPC sections 4.2, 4.4, 4.8, 5.1, 5.2, 6.2 and 6.6 were updated. The package leaflet was updated accordingly. The MAH initially proposed to extend the treatable wound area from 1 x 15% TBSA to 2 x 15% TBSA i.e. doubling the wound area for treatment to 30% TBSA in two treatment sessions. However, this was not agreed by CHMP as the safety database is currently considered insufficient and the submitted additional PK data are considered of minor relevance to support the extension of the treatable wound area from 1 x 15% TBSA to 2 x 15% TBSA. Thus, as stated in SmPC section 4.2, NexoBrid should not be applied to more than 15%. For more information, please refer to the Summary of Product Characteristics.

IB/0055/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	09/11/2021	n/a		
IB/0054	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/09/2021	n/a		
PSUSA/10028 /202012	Periodic Safety Update EU Single assessment - concentrate of proteolytic enzymes enriched in bromelain	02/09/2021	n/a		PRAC Recommendation - maintenance
IAIN/0053/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/importer responsible for batch release A.1 - Administrative change - Change in the name and/or address of the MAH	31/05/2021	21/06/2022	SmPC, Labelling and PL	
IA/0051/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	07/12/2020	n/a		

	product - Minor changes to an approved test procedure				
II/0050/G	This was an application for a group of variations. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for 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.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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	15/10/2020	n/a		
II/0047	Submission of the final study report for study MW2013-06-01, listed as a category 3 study in the RMP. This is an international, observational retrospective, data-collection study assessing efficacy of applied risk-minimisation measures in burn patients treated with NexoBrid. In addition, the	04/09/2020	n/a		The results from study MW2013-06-01 has achieved its primary goal and thus, the effectiveness of the implemented risk minimisation measures (RMMs) is considered shown. Even though only limited conclusions with respect to the extrapolation of the study results to non-participating EU countries are possible, the study

	MAH took the opportunity to revise the RMP in line with the new RMP template (GVP Rev. 2) and to change the due date for studies MW2013-06-01 and MW2010-03-02 (DETECT). The updated RMP version 7.1 is acceptable. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				provides evidence for a general effectiveness of the established additional RMMs.
IB/0048	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	29/05/2020	n/a		
IB/0046/G	This was an application for a group of variations. B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	27/02/2020	n/a		

IB/0045/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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/01/2020	n/a		
IB/0043	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	06/08/2019	n/a		
PSUSA/10028 /201812	Periodic Safety Update EU Single assessment - concentrate of proteolytic enzymes enriched in bromelain	11/07/2019	n/a		PRAC Recommendation - maintenance
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/06/2019	25/07/2019	PL	
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/04/2019	25/07/2019	Labelling and PL	
IA/0039	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	17/01/2019	n/a		
PSUSA/10028	Periodic Safety Update EU Single assessment -	26/07/2018	28/09/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending

/201712	concentrate of proteolytic enzymes enriched in bromelain				the variation to terms of the Marketing Authorisation(s)' for PSUSA/10028/201712.
IAIN/0038	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	09/08/2018	25/07/2019	Annex II and PL	
II/0035	Update of section 6.6 of the SmPC to change the instructions for NexoBrid gel preparation. The package leaflet is updated accordingly. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	07/06/2018	28/09/2018	SmPC and PL	The instructions for use in the product information for the NexoBrid gel preparation (mixing powder with the gel) have been updated to delete the need to shake vigorously the preparation to fragment the NexoBrid powder cake.
IB/0033	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/03/2018	n/a		
IB/0034	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	13/03/2018	n/a		
II/0032	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/01/2018	n/a		

R/0031	Renewal of the marketing authorisation.	14/09/2017	10/11/2017	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of NexoBrid in the approved indication remains favourable, and recommended the renewal of the marketing authorisation, but considered that another renewal in five years' time was needed based on the following pharmacovigilance grounds: an imposed additional pharmacovigilance study is ongoing, the results of which are expected to yield important new safety data which could impact on the benefit-risk balance of the product. Study MW2010-03-02, imposed at the time the initial MA was granted is outstanding and will study enzymatic debridement in burns patients (children and adults): a comparison to standard of care.
PSUSA/10028 /201612	Periodic Safety Update EU Single assessment - concentrate of proteolytic enzymes enriched in bromelain	20/07/2017	18/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10028/201612.
IB/0029	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	26/01/2017	n/a		
II/0027/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP -	10/11/2016	n/a		

	Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
PSUSA/10028 /201512	Periodic Safety Update EU Single assessment - concentrate of proteolytic enzymes enriched in bromelain	07/07/2016	n/a		PRAC Recommendation - maintenance
II/0025	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	18/02/2016	n/a		
PSUSA/10028 /201412	Periodic Safety Update EU Single assessment - concentrate of proteolytic enzymes enriched in bromelain	09/07/2015	n/a		PRAC Recommendation - maintenance
IAIN/0022	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	24/04/2015	n/a		

PSUV/0018	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IA/0019/G	This was an application for a group of variations. 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.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	30/10/2014	n/a		
IB/0017	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	04/08/2014	n/a		
PSUV/0011	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
IB/0012	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/06/2014	n/a		
IA/0016	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	18/06/2014	n/a		
IA/0015/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code B.II.e.6.b - Change in any part of the (primary)	18/06/2014	30/10/2014	SmPC	

	packaging material not in contact with the finished product formulation - Change that does not affect the product information				
II/0009	to change the immediate packaging of the gel vehicule B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	22/05/2014	30/10/2014	SmPC	
IB/0014/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.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	16/05/2014	n/a		
IB/0010	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	09/04/2014	n/a		
IA/0008	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	20/02/2014	n/a		

IA/0007	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	20/02/2014	n/a		
II/0006/G	This was an application for a group of variations. This was an application for a group of variations to change the specifications limits for viscosity and the procedure for the determination of viscosity. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	20/02/2014	n/a		
PSUV/0003	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IAIN/0005	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	29/11/2013	n/a		
IAIN/0004/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	29/10/2013	30/10/2014	SmPC, Annex II and PL	

	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 C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring				
T/0002	Transfer of Marketing Authorisation from Teva Pharma GmbH to MediWound Germany GmbH. Transfer of Marketing Authorisation	31/07/2013	19/09/2013	SmPC, Labelling and PL	
IAIN/0001	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/07/2013	n/a		