Beromun

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/0057	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	09/12/2021		Annex II	
IAIN/0056	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	23/06/2021	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).

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	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
PSUSA/2850/ 202008	Periodic Safety Update EU Single assessment - tasonermin	09/04/2021	n/a		PRAC Recommendation - maintenance
IAIN/0055	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	27/01/2021	n/a		
II/0051	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	10/12/2020	n/a		
II/0050	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	10/12/2020	n/a		
IAIN/0052	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	30/10/2020	n/a		
IAIN/0049	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	08/05/2020	n/a		

IAIN/0048	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	18/03/2020	23/07/2021	Annex II and PL	
IAIN/0047/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	12/03/2020	n/a		
IAIN/0046	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	10/01/2020	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IAIN/0045	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	03/12/2019	n/a		
IB/0043	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	08/11/2019	n/a		
IAIN/0042/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.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	19/07/2019	n/a		
IAIN/0041	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	13/06/2019	n/a		

T/0040	Transfer of Marketing Authorisation	17/07/2018	23/08/2018	SmPC, Labelling and PL	
IAIN/0039/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	04/07/2018	n/a		
PSUSA/2850/ 201708	Periodic Safety Update EU Single assessment - tasonermin	12/04/2018	n/a		PRAC Recommendation - maintenance
IAIN/0037/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes	25/08/2017	n/a		

	do not affect the properties of the FP				
IB/0035	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	03/07/2017	n/a		
IAIN/0036/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	16/05/2017	n/a		
IAIN/0034	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	27/02/2017	n/a		
IB/0033	B.II.z - Quality change - Finished product - Other variation	14/01/2017	03/10/2017	SmPC and PL	
IB/0032	B.II.a.6 - Deletion of the solvent/diluent container from the pack	27/09/2016	03/10/2017	SmPC, Labelling and PL	

IAIN/0031/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	28/07/2016	n/a		

IAIN/0030/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	03/08/2015	n/a		
PSUSA/2850/201408	Periodic Safety Update EU Single assessment - tasonermin	12/03/2015	n/a		PRAC Recommendation - maintenance
IB/0029/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.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.2.b - Change in the specification parameters	11/02/2015	n/a		

	and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method 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.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IG/0432	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	16/04/2014	n/a		
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/12/2013	03/10/2017	PL	
II/0025	Change in source of an excipient or reagent with TSE risk. B.II.c.3.b - Change in source of an excipient or reagent with TSE risk - Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability	21/11/2013	n/a		
II/0024	Update of section 4.8 of the SmPC to add the adverse reaction peripheral arterial occlusive disease	15/11/2012	20/11/2013	SmPC, Annex II, Labelling	Late onset of peripheral arterial occlusive disease (PAOD) of the lower limbs has been reported in patients several

	with a frequency uncommon at the request from the CHMP following the assessment of PSUR 10. The package Leaflet is updated accordingly. The MAH also took the opportunity to update the product information in line with the latest QRD template (version 8.1) and to update the list of local representatives in the Package leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH			and PL	years after ILP, predominantly in patients presenting with established cardiovascular risk factors, or who had undergone additional irradiation therapy of the concerned limb.
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		
II/0022/G	This was an application for a group of variations. Change in the specifications for the finished product. Change to in-process limits applied during the manufacture of the finished product. Change in test procedure for the finished product. 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.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	19/04/2012	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0020	Update of section 4.8 of the Summary of Product Characteristics (SmPC) further to a review of the methodology applied for the estimation of frequency of adverse reactions and extension of the safety dataset. Changes were also proposed to bring this section in line with the EU SmPC guideline. The Package leaflet has been updated accordingly. The Marketing Authorisation Holder (MAH) also proposed updates throughout the product information in line with the QRD template version 7.3.1 and the EU Guideline on Excipients including addition of information on the influence on human fertility to section 4.6 of the SmPC, a correction with regard to sodium chloride being an ingredient of the solvent and a warning in section 4.4 that the container of this medicinal product contains latex rubber. Editorial changes were also proposed throughout the product information. The MAH also took the opportunity to update the list of local representatives in the package leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	27/07/2011	SmPC, Labelling and PL	In order to allow a more robust estimation of frequency categories, the reference study data set was extended by adding three further studies in non-approved indication. The study design, doses, treatment duration and patient population in these studies were considered by the MAH to be comparable to the studies in the approved indication soft tissue sarcoma, which previously served as the basis for estimation of frequency categories. Reports of all studies had been provided in the original Marketing Authorisation Application for Beromun. Four new undesirable effects were identified which, however, in their underlying genesis did not fundamentally differ from the already known side effects (Abdominal pain upper, gastritis erosive, blood creatinine increased and pulmonary oedema). The extension of the reference study data as well as the change in methodology applied to frequency calculation resulted in a change in the frequency category for six previously listed undesirable effects. As a result of the changes described above, a complete revision and restructuring following the recommendations of the EU SmPC guideline was proposed for this section.
IB/0021/G	This was an application for a group of variations.	01/07/2011	n/a		

	B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) 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				
IB/0019/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.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	10/06/2011	n/a		

	procedure				
II/0018/G	This was an application for a group of variations. - Multiple changes to the manufacturing process of the active substance during both fermentation and purification aiming at optimizing the manufacturing process, changes to in-process tests and limits applied during the manufacture of the active substance - Multiple changes in test procedure, specification parameters and limits applied to cell banks, raw materials, biomass and active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol 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.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.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits	19/05/2011	19/05/2011		

	applied during the manufacture of the AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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.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.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.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.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.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS 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.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.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				

IA/0017	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	27/03/2009	n/a	Annex II and PL	
R/0015	Renewal of the marketing authorisation.	22/01/2009	25/03/2009	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of the re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Beromun continues to the favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity. PSURs will now be submitted every 3 years.
II/0013	Changes to the specifications for the active substance. Change(s) to the test method(s) and/or specifications for the active substance	25/09/2008	02/10/2008		
II/0012	Change(s) to the test method(s) and/or specifications for the active substance	28/06/2006	03/07/2006		
II/0011	Quality changes	18/11/2004	22/11/2004		
R/0010	Renewal of the marketing authorisation.	26/02/2004	17/06/2004	SmPC, Annex II, Labelling and PL	
II/0008	Update of Summary of Product Characteristics and Package Leaflet	25/09/2003	27/01/2004	SmPC and PL	

II/0009	Update of or change(s) to the pharmaceutical documentation	17/12/2003	23/12/2003		
II/0006	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	23/01/2003	28/01/2003		
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/12/2002	16/12/2002	PL	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	23/08/2001	28/01/2002	SmPC and PL	
I/0004	12_Minor change of manufacturing process of the active substance	16/11/2000	n/a		
I/0002	11_Change in or addition of manufacturer(s) of active substance	25/05/1999	29/07/1999	Annex II and PL	
I/0001	01_Change in the name of a manufacturer of the medicinal product	25/05/1999	29/07/1999	Annex II and PL	
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/05/1999	29/07/1999	PL	