Mepact

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
IA/0059	A.7 - Administrative change - Deletion of manufacturing sites	19/12/2023		Annex II and PL	
IB/0058	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)	12/07/2023		SmPC 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).

IB/0056	A.z - Administrative change - Other variation	28/04/2023	n/a		
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/04/2023		PL	
IB/0055	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	20/02/2023	n/a		
PSUSA/2059/ 202203	Periodic Safety Update EU Single assessment - mifamurtide	27/10/2022	n/a		PRAC Recommendation - maintenance
IA/0054	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	17/10/2022	n/a		
IB/0052/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.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.z - Quality change - Finished product - Other variation	18/02/2022	n/a		
IB/0051	B.IV.1.z - Change of a measuring or administration device - Other variation	20/08/2021	n/a		

IAIN/0050	A.1 - Administrative change - Change in the name and/or address of the MAH	22/04/2020	21/04/2021	SmPC, Labelling and PL	
PSUSA/2059/ 201903	Periodic Safety Update EU Single assessment - mifamurtide	17/10/2019	16/12/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2059/201903.
IB/0048/G	This was an application for a group of variations. B.II.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	27/03/2019	n/a		
R/0047	Renewal of the marketing authorisation.	13/12/2018	20/02/2019	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considers that there are no grounds to change the currently favourable benefit-risk balance of Mepact in the approved indication. Therefore, it is recommended the marketing authorisation is renewed with unlimited validity.
IA/0046	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	07/02/2017	n/a		
IAIN/0044/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	14/12/2016	10/11/2017	SmPC, Annex II and PL	

	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.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release 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				
IA/0045/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.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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	09/12/2016	n/a		
PSUSA/2059/ 201603	Periodic Safety Update EU Single assessment - mifamurtide	29/09/2016	n/a		PRAC Recommendation - maintenance
IB/0043	C.I.11.z - Introduction of, or change(s) to, the	12/09/2016	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IAIN/0041	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	28/01/2016	n/a		
IAIN/0040/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) A.7 - Administrative change - Deletion of manufacturing sites 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	17/12/2015	23/12/2016	Annex II and PL	
PSUSA/2059/201503	Periodic Safety Update EU Single assessment - mifamurtide	10/09/2015	n/a		PRAC Recommendation - maintenance
IA/0039	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/06/2015	n/a		

PSUV/0037	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IAIN/0036	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	12/02/2014	n/a		
R/0034	Renewal of the marketing authorisation.	24/10/2013	18/12/2013	SmPC, Annex II and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considers by consensus that the risk-benefit balance of Mepact in the treatment of ” high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults used in combination with post-operative multi-agent chemotherapy remains favourable and therefore recommends the renewal of the marketing authorisation under exceptional circumstances. The CHMP also recommends that one additional five-year renewal be required based on the limited post-marketing experience with Mepact, encompassing 415 patients in clinical practice to date. In addition the patient recruitment in the non-interventional surveillance study (C23003) tto assess the short and long-term safety profile of Mepact is slow, with only 12 patients included to date. Pursuant to Article 3 of Commission Regulation (EC) No 2141/96, the Marketing Authorisation Holder submitted to the Agency on 02 July 2013 an application for the transfer of the Marketing Authorisation to Takeda France SAS, which received a positive EC decision during the evaluation

					of the current MA renewal.
T/0035	Transfer of Marketing Authorisation	01/08/2013	05/09/2013	SmPC, Labelling and PL	
IB/0032/G	This was an application for a group of variations. 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.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	19/06/2013	n/a		
IAIN/0033	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	10/06/2013	05/09/2013	Annex II and PL	
IA/0031/G	This was an application for a group of variations. 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 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	31/05/2013	n/a		
IB/0029/G	This was an application for a group of variations.	22/05/2013	n/a		

	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.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.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.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				
IAIN/0028	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/04/2013	n/a		
II/0026	Update of section 5.2 of the SmPC with information on pharmacokinetics of mifamurtide following the assessment of the final PK/PD report of the study MTP-OS-403 (FUM003). Furthermore, the PI is being brought in line with the latest QRD template version 8.3.	21/03/2013	05/09/2013	SmPC and Annex II	The pharmacokinetics of mifamurtide has been characterized in paediatric and adult patients with osteosarcoma following a 2 mg/m2 intravenous infusion. In 28 osteosarcoma patients aged 6 to 39 years serum total (liposomal and free) mifamurtide concentrations declined rapidly with a mean half-life of 2.04 ± 0.456 hours. BSA-normalized clearance and half-life were similar

	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				across the age range and consistent with that determined in healthy adult subjects, supporting the recommended dose of 2 mg/m2. Metabolism of L-MTP-PE has not been studied in humans. After injection of radiolabelled liposomes containing mifamurtide, mean half-life of radiolabelled material was biphasic with an α phase of about 15 minutes and a terminal half-life of approximately 18 hours. The SmPC has been updated to reflect the above results.
IA/0027/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 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 currently approved batch size	01/02/2013	n/a		
II/0025	Update of sections 4.2 and 5.2 of the SmPC with information on the pharmacokinetics of Mepact in patients with renal and hepatic impairment following the assessment of the clinical study reports for studies C23001 and C23002, respectively. In addition, section 4.9 of the SmPC was updated with a reported case of overdose. This type II variation fulfils the post-authorisation measure FUM/004. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	05/09/2013	SmPC	Based on the results from C23001 and C2302 studies there are no clinically meaningful effects of mild to moderate renal (creatinine clearance (CrCL) ≥ 30ml/min) or hepatic impairment (Child-Pugh class A or B) on the pharmacokinetics of mifamurtide; therefore, dose adjustments are not necessary for these patients. However, as the variability in pharmacokinetics of mifamurtide is greater in subjects with moderate hepatic impairment, and safety data in patients with moderate hepatic impairment is limited, caution when administering mifamurtide to patients with moderate hepatic impairment is recommended. As no pharmacokinetic data of mifamurtide is available in patients

					with severe renal or hepatic impairment, caution when administering mifamurtide to these patients is recommended. Section 4.2 of the SmPC has been updated with the above information and the results of the PK studies have been added in section 5.2 of the SmPC. Finally section 4.9 of the SmPC has been updated to include that a healthy adult volunteer accidentally received a single dose of 6.96 mg mifamurtide and experienced a reversible treatment-related event of orthostatic hypotension.
II/0024	Update of section 4.8 of the SmPC in order to include febrile neutropenia as common adverse reaction further to the assessment of the 5th PSUR. The Package Leaflet is updated accordingly. 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	19/07/2012	23/08/2012	SmPC and PL	As of 5 March 2012 there were 205 patients who received mifamurtide in the clinical study (MTP OS-403) and approximately 171 patients who received mifamurtide during the post marketing experience. The frequency of febrile neutropenia from clinical studies is 1.5% (n=3) and the post marketing frequency is reported as 0.6% (n=1). For all three cases of febrile neutropenia reported in the clinical studies there were, besides mifamurtide use, additional factors that might also contributed to the events (i.e. concomitant use of ifosfamide, etoposide, concurrent toe cellutitis and recurrent febrile). Limited information (concomitant medications, medical history) was available for the one spontaneous reported febrile neutropenia case.
A20/0022	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 17 November 2011, the opinion of the CHMP on measures necessary to ensure the quality and the safe use of the above mentioned medicinal product further to the inspection findings at the Ben Venue Laboratories (BVL) manufacturing site located in	19/02/2012	25/05/2012		Please refer to the assessment report: EMEA/H/C/802/A20/0022

	Bedford, Ohio (USA).				
IA/0023/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS 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 batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place A.7 - Administrative change - Deletion of manufacturing sites	26/04/2012	n/a		
IB/0021/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation A.7 - Administrative change - Deletion of manufacturing sites	21/10/2011	n/a		
IB/0020/G	This was an application for a group of variations.	08/09/2011	n/a		

	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.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation				
IB/0019/G	This was an application for a group of variations. 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.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	08/09/2011	n/a		
IA/0017	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)	06/05/2011	n/a		
IB/0016	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	07/01/2011	n/a		

IB/0015	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)	05/01/2011	n/a	SmPC, Annex II, Labelling and PL	
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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS 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 batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place 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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/12/2010	n/a		
IA/0014/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	23/08/2010	n/a	Annex II and PL	

	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing				
IA/0012	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	27/07/2010	n/a		
IB/0011	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	26/07/2010	n/a		
IA/0010/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 C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the	16/07/2010	n/a	Annex II	

	DD 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				
IA/0009	A.1 - Administrative change - Change in the name and/or address of the MAH	05/03/2010	n/a	SmPC, Labelling and PL	
IA/0007	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	18/01/2010	n/a	Annex II and PL	
IA/0006	To change the content calculation of excipient OOPS IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	18/12/2009	n/a		
IA/0005	To change reference standard in assay. IA_13_a_Change in test proc. for active substance - minor change	18/12/2009	n/a		
IA/0004	To change the cap colour specification for Mepact finished product. IA_28_Change in any part of primary packaging material not in contact with finished product	18/12/2009	n/a		

IA/0003	To add a new testing site for Mepact finished product (EU/1/08/502/001). IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	18/12/2009	n/a		
IA/0002	To replace a testing site for unlabelled finished product. IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	18/12/2009	n/a		
IA/0001	To replace manufacturing site for secondary packaging activities regarding Mepact Finished product IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/12/2009	n/a		