Halaven

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/0065/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or	09/11/2022		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).

	reconstitution (supported by real time data)				
IB/0064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/05/2022	n/a		
IB/0063	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/04/2022	n/a		
IB/0061	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/02/2022		SmPC, Annex II and PL	
IA/0062	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	23/02/2022	n/a		
II/0060	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update efficacy and pharmacokinetic information based on results from clinical studies E7389-A001-113, E7389-G000-223 and E7389-G000-213 in the paediatric population (6 months to <18 years); the Package Leaflet is updated accordingly. The RMP version 6.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/02/2022	02/06/2022	SmPC and PL	SmPC new text There is no relevant use of HALAVEN in the paediatric population for the indication of soft tissue sarcoma. Three open-label studies, Studies 113, 213 and 223, were conducted in paediatric patients with refractory or recurrent solid tumours and lymphomas, but excluding central nervous system (CNS) tumours. Efficacy of eribulin was assessed but not established in the three open-label studies. The safety profile of eribulin as monotherapy or in combination with irinotecan hydrochloride in this paediatric population was consistent with the known safety profile of either study drug in the adult population. Eribulin PK in paediatric patients was comparable to adult patients with STS and patients with other types of tumour. Eribulin exposure in paediatric patients was similar to exposure in adult patients. Concomitant irinotecan did not have an

					effect on eribulin PK in paediatric patients with refractory/relapsed and recurrent solid tumours. For more information, please refer to the Summary of Product Characteristics.
PSUSA/1254/ 202011	Periodic Safety Update EU Single assessment - eribulin	08/07/2021	n/a		PRAC Recommendation - maintenance
IA/0058/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	02/03/2021	18/03/2022	Annex II and PL	
IB/0057	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/01/2021	04/02/2021	SmPC and PL	
IB/0056	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/08/2020	n/a		
IA/0054	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	29/06/2020	n/a		

	manufacturer of a novel excipient				
IAIN/0055	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	24/06/2020	04/02/2021	Annex II and PL	
IAIN/0053/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.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	24/06/2020	04/02/2021	SmPC, Labelling and PL	
IAIN/0052	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	28/01/2019	n/a		
II/0047	Update of section 4.4 and 4.8 of the SmPC in order to add information on Hypocalcaemia and to add it as new adverse reaction with frequency 'common' as a result of a cumulative review on the matter requested during the EMEA/H/C/PSUSA/00001254/201711 procedure (LEG 021). C.I.3.b - Change(s) in the SPC, Labelling or PL	24/01/2019	24/10/2019	SmPC and PL	Hypokalaemia, hypocalcaemia or hypomagnesaemia should be corrected prior to initiating HALAVEN and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome.

	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 new additional data submitted by the MAH				
IG/1008	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	30/11/2018	24/10/2019	Annex II and PL	
IA/0051	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	27/11/2018	n/a		
IB/0048	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	24/10/2018	n/a		
IA/0049/G	This was an application for a group of variations. B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients B.II.e.2.c - Change in the specification parameters	18/10/2018	n/a		

	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)				
T/0046	Transfer of Marketing Authorisation	23/08/2018	28/09/2018	SmPC, Labelling and PL	
IAIN/0044	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	30/07/2018	n/a		
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2018	28/09/2018	Labelling and PL	
PSUSA/1254/ 201711	Periodic Safety Update EU Single assessment - eribulin	14/06/2018	n/a		PRAC Recommendation - maintenance
IB/0041/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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.a - Changes in the manufacturing process of	06/12/2017	n/a		

	the AS - Minor change in the manufacturing process of the AS				
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/11/2017	30/07/2018	PL	
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)	17/08/2017	30/07/2018	SmPC	
PSUSA/1254/ 201611	Periodic Safety Update EU Single assessment - eribulin	09/06/2017	n/a		PRAC Recommendation - maintenance
IA/0039	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	17/05/2017	n/a		
II/0033	Update of the RMP version 4.2 following the revision of the protocol for a post-authorisation study to capture data on the frequency of resolution and time to resolution of eribulin-induced or -aggravated peripheral neuropathy in patients from a phase 3 study, E7389-A001-303 (ACCRU); the MAH will instead conduct an observational study, E7389-M044-504 (IRENE). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	21/04/2017	n/a		

	where significant assessment is required				
IA/0036	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	24/02/2017	n/a		
IB/0034	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	30/11/2016	n/a		
PSUSA/1254/ 201511	Periodic Safety Update EU Single assessment - eribulin	23/06/2016	16/08/2016	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1254/201511.
IB/0032/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.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.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	20/07/2016	n/a		

	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.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.f.1.e - Stability of FP - Change to an approved stability protocol				
II/0028	Extension of Indication to include the treatment of unresectable liposarcoma in adult patients who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated with the PK, efficacy and safety information. The Package Leaflet and RMP are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the PI in line with the latest QRD template version 9.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	01/04/2016	02/05/2016	SmPC and PL	Please refer to the Scientific Discussion Halaven-H-C-2084-II-028.
II/0029/G	This was an application for a group of variations. Update of section 4.4 of the SmPC to remove the information referring to the lack of data on safety and efficacy of eribulin in combination with anti-HER2 therapy. Moreover, the MAH deleted the black	18/02/2016	02/05/2016	SmPC and PL	

	symbol and explanatory statements pertinent to the additional monitoring as Halaven has been removed from the list of the medicinal products subject to the additional monitoring. In addition, the MAH took the opportunity of this procedure to update the local representative contact of Romania in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0027	Renewal of the marketing authorisation.	24/09/2015	19/11/2015	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 that the benefit/risk profile of Halaven continues to be favourable. The CHMP is of the opinion that the renewal can be granted with unlimited validity.
IA/0030	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)	09/09/2015	n/a		
II/0024	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	23/07/2015	n/a		

PSUSA/1254/201411	Periodic Safety Update EU Single assessment - eribulin	21/05/2015	17/07/2015	SmPC and PL	Please refer to Halaven PSUSA-00001254-201411 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
IA/0026	A.7 - Administrative change - Deletion of manufacturing sites	01/07/2015	n/a		
II/0023	Update of sections 4.2 and 5.2 of the SmPC to include further recommendations for patients with renal impairment based on data from Study 106. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and to update the contact details of the local representatives in Belgium, Luxemburg and Poland in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	19/11/2015	SmPC and PL	Some patients with moderately or severely impaired renal function (creatinine clearance <50 ml/min) may have increased eribulin exposure and may need a reduction of the dose. For all patients with renal impairment, caution and close safety monitoring is advised. Increased eribulin exposure was seen in some patients with moderately or severely impaired renal function, with high between-subject variability. The pharmacokinetics of eribulin were evaluated in a Phase 1 study in patients with normal renal function (Creatinine clearance: ≥ 80 ml/min; n=7), moderate (30-50 ml/min; n=6) or severe (15-<30 ml/min; n=6) renal impairment. Creatinine clearance was estimated with the Cockroft-Gault formula. A 1.5-fold (90% CI: 0.9-2.5) higher dose-normalised AUC(0-inf) was observed in patients with moderate and severe renal impairment.
IB/0025	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	13/04/2015	17/07/2015	SmPC and Labelling	
II/0021	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of	26/02/2015	17/07/2015	SmPC, Labelling and	

	sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products			PL	
IA/0020	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	01/12/2014	n/a		
IA/0019	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	30/07/2014	n/a		
II/0011	Extension of Indication to include the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease. As a consequence, sections 4.1, 4.5, 4.8, 5.1 of the SmPC were updated. The Package Leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/05/2014	27/06/2014	SmPC and PL	Please refer to the Scientific Discussion Halaven EMEA/H/C/002084/II/0011.
PSUV/0018	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
IA/0017	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	27/02/2014	n/a		

	changes to an approved test procedure				
IA/0015	A.7 - Administrative change - Deletion of manufacturing sites	18/12/2013	n/a		
II/0014	Update of sections 4.2, 4.5 and 5.2 of the SmPC in order to reflect the results of studies investigating the use of eribulin in patients with renal impairment, interactions with Pgp inhibitors and whether eribulin is a substrate of hepatic transporters, as requested by PRAC/CHMP further to the review of FUMs 009, 010, 011 and 013. 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 new additional data submitted by the MAH	18/12/2013	27/06/2014	SmPC	Analyses performed across Phase I studies show that patients with severely impaired renal function may require a reduction of dose however the optimal dose remains to be established. In patients with mild to moderate renal impairment, caution and close safety monitoring is advised without recommendation for specific dose adjustments. Eribulin is mainly eliminated through biliary excretion. In vivo studies submitted by the MAH show that eribulin exposure (AUC and Cmax) was not affected by Pgp inhibitors. In addition, on the basis of in vitro studies, it was concluded thateribulin is not a Pgp inhibitor and is not considered as a substrate for OCT1. As a consequence, sections 4.2, 4.5 and 5.2 of the SmPC were updated to reflect new information.
IA/0016	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	13/12/2013	n/a		
IG/0345	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	03/09/2013	n/a		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2013	20/11/2013	PL	

II/0009	Update of section 4.8 of the SmPC in order to update the safety information to include disseminated intravascular coagulation (DIC) as an adverse drug reaction further to the PRAC review of PSUR 3. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0. 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	25/04/2013	20/11/2013	SmPC, Annex II and PL	Further to the review of the company safety database with a data lock point of 14th November 2012, the MAH identified 4 case reports of DIC. While a direct causal relationship cannot be established at this point in time, there is enough circumstantial evidence to conclude that a causal relationship between eribulin and DIC is at least a reasonable possibility. Section 4.8 of the SmPC was updated to include DIC as a rare event.
IAIN/0010	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/03/2013	n/a		
IB/0008/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a	22/11/2012	n/a		

	starting material/reagent/intermediate for AS - Other variation 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				
II/0006	Update of section 4.5 of the SmPC in order to reflect new data regarding concomitant use with inhibiting and inducing substances. Furthermore, the PI is being brought in line with the latest QRD template version 8.1. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	20/11/2013	SmPC, Annex II, Labelling and PL	Following the review of a drug-drug interaction study investigating the effect of concomitant use of rifampicin and eribulin versus eribulin alone, the MAH has updated section 4.5 of the SmPC to reflect new data on inhibiting and inducing substances.
IB/0007	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	08/08/2012	n/a		
II/0005	Update of sections 2, 4.2, 4.9, 5.1, 5.2, 5.3 and 6.3 of the SmPC to clarify the expression of the strength and dosage of Halaven to be administered to patients. This update has been triggered by concerns of potential risk of overdose related to the confusion between the use of eribulin base for the expression of the strength and dose in the EU compared to the use of the salt (mesilate) in a number of other	19/04/2012	22/05/2012	SmPC, Labelling and PL	Following reports of potential risk of overdose related to the confusion between the use of eribulin base for the expression of the strength and dose in the EU compared to the use of the salt (mesilate) in a number of other countries and in the scientific literature, the MAH was requested to amend the product information (PI) to express eribulin strength and dose consistently using the eribulin base and to avoid altogether the expression of these based

	countries and in the scientific literature. The Labelling and Package Leaflet have been updated accordingly. In addition, the MAH took the opportunity of this variation to make a minor amendment to section 4.8 of the SmPC, to correct the spelling of the salt 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				on the eribulin mesilate salt throughout the PI.
II/0004	Update of section 4.8 Undesirable effects of the SmPC in order to include pancreatitis as requested by the CHMP following the assessment of the 1st PSUR. The Package Leaflet was updated in accordance. In addition, the text and format of the table of undesirable effects in section 4.8 of the SmPC has been changed to include the uncommon and rare events into the one table. Finally the MA date and numbers have been added to sections 8 and 9 of the SmPC. 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	15/03/2012	20/04/2012	SmPC and PL	In the 1st PSUR of Halaven, two cases of pancreatitis were reported, one of which fulfilling the criteria for a very likely/certain drug reaction. As an outcome of the PSUR assessment, the CHMP requested the MAH to add pancreatitis in section 4.8 Undesirable effects. The Package leaflet was updated in accordance. The table of undesirable effects in section 4.8 of the SmPC was reformatted to include the uncommon and rare events already present in the section.

	MAH				
II/0003/G	This was an application for a group of variations. Addition of manufacturing, quality control and testing sites for the finished product. Minor differences in the manufacturing process at the new manufacturing site. 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.3.z - Change in the manufacturing process of the finished product - Other variation B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection 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.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.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	16/02/2012	16/02/2012		

IA/0002	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	22/09/2011	n/a		
IB/0001	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	09/09/2011	n/a		