Zavesca

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/0072/G	This was an application for a group of variations. Update of sections 4.4, 4.6 and 5.3 of the SmPC in order to improve clarity and to implement linguistic changes following an update of the non-clinical information in the MAH's Company Core Data Sheet.	01/07/2021		SmPC, Annex II, Labelling and PL	For more information, please refer to the Summary of Product Characteristics.

[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).

	In addition, the MAH took the opportunity to make editorial changes in the Annexes, and to update the list of local representatives in the Package Leaflet. The application also includes a type IA variation in order to delete one of the manufacturing sites responsible for batch release: Actelion Manufacturing GmbH. Annex II is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data A.7 - Administrative change - Deletion of manufacturing sites				
IB/0071	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/11/2020	08/02/2021	SmPC and PL	
N/0070	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/10/2020	08/02/2021	PL	
IAIN/0069/G	This was an application for a group of variations. 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 -	21/02/2020	08/02/2021	Annex II and PL	

	Not including batch control/testing				
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/12/2019	08/02/2021	PL	
IAIN/0068/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.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	10/10/2019	n/a		
PSUSA/2062/ 201810	Periodic Safety Update EU Single assessment - miglustat	16/05/2019	n/a		PRAC Recommendation - maintenance
IB/0065/G	This was an application for a group of variations. 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.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	15/02/2019	n/a		

N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/11/2018	08/02/2021	PL	
T/0063	Transfer of Marketing Authorisation	23/08/2018	28/09/2018	SmPC, Labelling and PL	
II/0062/G	This was an application for a group of variations. 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 where significant assessment is required C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/07/2018	n/a		
PSUSA/2062/ 201710	Periodic Safety Update EU Single assessment - miglustat	17/05/2018	n/a		PRAC Recommendation - maintenance
N/0061	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/05/2018	06/07/2018	Labelling and PL	
IB/0059	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/12/2017	n/a		
IG/0839	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	20/11/2017	06/07/2018	SmPC, Annex	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing			II and PL	
II/0057	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 where significant assessment is required	28/09/2017	n/a		
II/0056	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	06/07/2018	SmPC, Annex II, Labelling and PL	
PSUSA/2062/ 201610	Periodic Safety Update EU Single assessment - miglustat	05/05/2017	n/a		PRAC Recommendation - maintenance
IG/0720	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	16/08/2016	19/07/2017	Annex II and PL	
II/0052/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.I.b.1.b - Change in the specification parameters	23/06/2016	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP				
PSUSA/2062/ 201510	Periodic Safety Update EU Single assessment - miglustat	13/05/2016	n/a		PRAC Recommendation - maintenance
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/10/2015	08/08/2016	PL	
IG/0612	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	07/09/2015	08/08/2016	Annex II and PL	
PSUSA/2062/ 201410	Periodic Safety Update EU Single assessment - miglustat	07/05/2015	n/a		PRAC Recommendation - maintenance
II/0046	Changes in the manufacturing process of the active substance. 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	24/07/2014	n/a		

	medicinal product				
PSUV/0044	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/04/2014	27/10/2014	PL	
IB/0043	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/11/2013	27/10/2014	SmPC, Annex II and PL	
N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/07/2013	27/10/2014	PL	
IB/0040/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.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)	01/02/2013	12/08/2013	SmPC	
IAIN/0041	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/01/2013	n/a		
R/0037	Renewal of the marketing authorisation.	21/06/2012	08/10/2012		
IAIN/0038/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name	04/10/2012	12/08/2013	SmPC, Labelling and PL	

	and/or address of the MAH C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
S/0036	Annual reassessment.	19/04/2012	23/08/2012		The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable. The CHMP considered that, as all Specific Obligations have been fulfilled, there are no remaining grounds for the Marketing Authorisations to remain under exceptional circumstances.
II/0034	The MAH updated sections 4.4, 4.7, 4.8, and 5.1 of the SmPC in order to include new information on the results from clinical studies performed in fulfilment of two specific obligations. The Package Leaflet (sections 2 and 4) was updated in accordance. Annex II, section IIC, was updated accordingly to reflect the requested fulfilment of the specific obligations SO2 and SO3. Minor linguistic improvements in the Polish Annexes I–III of Zavesca are made. Minor changes in the wording of section 4.4 of the SmPC were also implemented in order to improve clarity. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the MAH used this opportunity to bring the PI in line with the QRD template version 7.3. The requested variation proposed amendments to the SmPC and Package Leaflet.	17/11/2011	22/12/2011	SmPC, Annex II and PL	This variation concerns amendment of Product Information for Zavesca based on the results obtained from the two recently completed studies (OGT 918-011 and OGT 918-018) and from the analysis of the updated pooled safety data. The results were submitted in fulfilment of specific obligations SO2 and SO3. Section 5.1 of the SmPC was amended to add information obtained from study OGT 918-011, which was an open-label, non comparative, 2-year study enrolled 42 patients with type 1 Gaucher disease, who had received a minimum of 3 years of ERT and who fulfilled criteria of stable disease for at least 2 years. The patients were switched to monotherapy with miglustat 100 mg t.i.d. Liver volume (primary efficacy variable) was unchanged from baseline to the end of treatment. Six patients had miglustat treatment prematurely discontinued for potential disease worsening, as defined in the study. Twenty-one patients completed 24 months of miglustat treatment. Of these, 18 patients at

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				baseline were within established therapeutic goals for liver and spleen volume, haemoglobin levels, and platelet counts, and 16 patients remained within all these therapeutic goals at Month 24. In section 4.4 of the SmPC, information about the need to re-assess risk-benefit in patients who develop symptoms such as numbness and tingling is deleted and this is based on the results of studies OGT 918-011 and OGT 918-018. Section 4.8 and 4.7 were updated with information related tt adverse events and their frequency, as observed in the above studies.
IAIN/0035	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	28/11/2011	n/a		
S/0033	Annual Re-assessment	17/03/2011	16/05/2011	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
S/0032	Annual re-assessment.	18/03/2010	02/06/2010		
IB/0031	IB_38_c_Change in test procedure of finished product - other changes	09/12/2009	n/a		
S/0030	Annual re-assessment.	19/03/2009	26/05/2009	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, concluded

					that, overall, the benefit/risk ratio for the product remains unchanged. The list of Specific obligations was revised according to the conclusions of the CHMP discussion. The CHMP considered that the Marketing Authorisation for Zavesca should remain under exceptional circumstances in view of the pending Specific Obligations.
II/0029	Extension of Indication	18/12/2008	26/01/2009	SmPC, Annex II and PL	Please refer to Scientific Discussion Zavesca H/C/435/II/0029.
II/0028	Update of sections 4.4 and 5.1 of the Summary of Product Charecteristics (SPC), to reflect the wider clinical experience available since the marketing authorisation of miglustat. In addition the Package Leaflet was updated to reflect the new contact details of a number of local representatives. Update of Summary of Product Characteristics and Package Leaflet	25/09/2008	28/10/2008	SmPC and PL	With this variation the MAH submitted the results of an extension of study OGT 918-004 and of a pooled analysis on the effect of miglustat on bone disease from three clinical trials (OGT 918-001, OGT 918-004, OGT 918-005). Furthermore, the MAH provided a discussion on the comparability between miglustat and intravenous enzyme replacement treatment (ERT) as well as on the severity assessment at baseline in patients treated with miglustat. Addition of descriptive data to section 5.1 was seen as adding value to the prescriber and was therefore recommended by the CHMP. Finally, the CHMP endorsed the changes to aspects of the wording covering on the comparison between miglustat and ERT and for experience in severely affected patients.
S/0027	Annual re-assessment.	19/03/2008	20/05/2008	Annex II	
II/0026	Update of sections 4.8 of the Summary of Products Characteristics (SPC) to reflect the wider safety database following the 6th Periodic Safety Update	21/02/2008	18/03/2008	SmPC and PL	A pooled analysis of safety data has been performed for all clinical trials with miglustat and for the type I Gaucher disease indication. Also data from an observational study in

	Report (PSUR)/4th Annual Reassessment. Peripheral neuropathy and cognitive disturbance have been included in section 4.8 of the SPC and a corresponding warning for peripheral neurophathy has been included in section 4.4 of the SPC based on data from an observational study. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				patients with type 1 Gaucher disease not exposed to miglustat were submitted. Considering that only one case of cognitive function was reported as related to treatment at the time of the initial marketing authorisation, and that no additional reports have been obtained, neither in clinical trials nor in the Periodic safety Update Reports, the warning in section 4.4 of the SPC concerning the recommendation for periodic assessment of cognitive function has been deleted. The results from trial OGT 918-018 indicate that peripheral neuropathy may be more common in patients with type 1 Gaucher disease compared to the general population, and therefore section 4.4 of the SPC has been updated to reflect this information. A section concerning exposure and incidence across different patient groups has been included in section 4.8 of the SPC as well as reclassification of several adverse drug reactions. The Package Leaflet has been updated accordingly.
II/0025	Change(s) to the manufacturing process for the active substance	13/12/2007	19/12/2007		
II/0021		18/10/2007	n/a		
R/0024	Renewal of the marketing authorisation.	21/06/2007	07/09/2007	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a 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 Zavesca continues to be favourable but its safety profile is to be monitored.

					There are still ongoing studies (including the post marketing surveillance plan) which will provide further information on the safety of Zavesca, including information on neurological, neuropsychological and gastrointestinal effects. Due to potential safety issues the CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the above safety concern of Zavesca, the submission of yearly PSURs is required. The CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
S/0023	Annual re-assessment.	22/03/2007	22/05/2007	SmPC and PL	"The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, concludes that, overall, the benefit/risk ratio for the product remains unchanged. Amendments were made to section 5.2 and section 4.8 of the SPC. The PL has also been amended (changes in details of local representatives). The CHMP considered that the Marketing Authorisation for Zavesca should remain under exceptional circumstances in view of the pending Specific Obligations."
II/0019	Update of section 5.3 of the Summary of Product Characteristics (SPC) following the fulfillment of two Follow-Up Measures: a 104-week mouse carcinogenicity study and a 2-year rat carcinogenicity study. This led also to amendments in sections 4.4	24/01/2007	28/02/2007	SmPC and PL	The section 5.3 of the SPC has been updated with the results of two rodent carcinogenicity studies which have been finalised: a 104-week mouse carcinogenicity study and a 2-year rat carcinogenicity study. In the mouse study there were an increased incidence of inflammatory and

	and 4.8 of the SPC and to section 2 of the Package Leaflet. In addition, contact details of Bulgarian and Romanian local representatives were also included. Update of Summary of Product Characteristics and Package Leaflet				hyperplastic lesions in the large intestine. The doses corresponded to 16, 32 and 65/38 times the recommended human dose. Carcinomas in large intestine occurred occasionally at all doses with a statistically significant increase in the high dose group. In view of these results the MAH also discussed the human gastrointestinal safety of Zavesca on the basis of data from clinical trials and post-marketing experience. The evaluation of these data led to an update of the warnings in relation to gastrointestinal effects, mainly diarrhoea including recommendations for further investigation of patients with chronic diarrhoea or other persistent gastrointestinal events. Section 2 of the PL has also been updated to reflect this warning.
IA/0020	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/10/2006	n/a		
II/0016	Change(s) to the test method(s) and/or specifications for the finished product	21/09/2006	27/09/2006		
IA/0018	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	25/07/2006	n/a	Annex II and PL	
IA/0017	IA_39_Change/addition of imprints, bossing or other markings	25/07/2006	n/a	SmPC, Labelling and PL	
S/0015	Annual re-assessment.	23/02/2006	24/04/2006	Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, concluded

					that, overall, the benefit/risk ratio for the product remains unchanged. Amendments were made to the Package Leaflet (changes in contact details of local representatives). The list of Specific obligations and was revised according to the conclusions of the CHMP discussion. The CHMP considered that the Marketing Authorisation for Zavesca should remain under exceptional circumstances in view of the pending Specific Obligations.
IB/0013	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	27/10/2005	n/a		
IA/0014	IA_09_Deletion of manufacturing site	11/10/2005	n/a		
N/0012	The approved EU packaging for Zavesca consists of: Four blisters, four calendar cards, four blister holders and one Package Leaflet are assembled together with an outer carton to form a booklet. The MAH has removed the calendar cards and blister holders from the packaging. The pictogram and the three steps for removal of the capsules have been transferred from the blister holders to section 3 of the Package Leaflet ("How to take Zavesca). The text "Morning, Afternoon, Evening" in the calendar card has also been transferred to section 3 of the Package Leaflet, which now states, "the usual dose is one capsule (100 mg) three times a day (morning, afternoon, evening)". The calendar card text Day 1 -	23/09/2005	n/a	Labelling and PL	

	day 7 has been deleted. Additionally, the pictogram "ZA" in front of the invented name has been eliminated in a few places from the outer carton. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
S/0011	Annual re-assessment.	17/03/2005	03/06/2005	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, concluded that, overall, the benefit/risk ratio for the product remains unchanged. Amendments were made to SPC and PL. Some minor changes were also included both in the SPC and PL in accordance to the latest EMEA templates. The CHMP considered that the Marketing Authorisation for Zavesca should remain under exceptional circumstances in view of the pending Specific Obligations.
IB/0010	IB_38_c_Change in test procedure of finished product - other changes	11/01/2005	n/a		
IB/0008	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	06/12/2004	n/a	SmPC	
IB/0006	IB_17_a_Change in re-test period of the active substance	06/12/2004	n/a		

IB/0007	IB_17_b_Change in the storage conditions for the active substance	08/11/2004	n/a		
IA/0009	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/10/2004	n/a	Annex II and PL	
IA/0005	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	14/10/2004	n/a		
S/0004	Annual re-assessment.	26/02/2004	18/08/2004	Annex II	The CPMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, concludes therefore that, overall, the benefit/risk ratio for the product remains unchanged and recommends that no amendment of Annexes I and III of the Commission Decision is necessary. The Marketing Authorisation for Zavesca should remain under exceptional circumstances in view of the pending Specific Obligations.
I/0003	03_Change in the name and/or address of the marketing authorisation holder	01/09/2003	08/10/2003	SmPC, Labelling and PL	
I/0002	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	09/04/2003	22/04/2003		
T/0001	Transfer of Marketing Authorisation	16/12/2002	03/02/2003	SmPC, Labelling and PL	