Imlygic

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/0057	Update to sections 4.4 and 4.8 of the SmPC to revise the safety instructions regarding the risk of disseminated herpetic infection adverse drug reactions following an MAH review of aggregate safety data of herpetic and disseminated herpetic infections that were reported in patients who were	13/10/2022		SmPC and PL	SmPC new text Disseminated herpetic infection, including serious cases of disseminated herpetic infection, have been reported in patients treated with Imlygic (see SmPC section 4.8). Based on epidemiological data, immunocompromised patients (such as those with HIV/AIDS, leukaemia,

[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).

	not immunocompromised and those who were immunocompromised. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				lymphoma, common variable immunodeficiency, or who require chronic high-dose steroids or other immunosuppressive agents) may be at increased risk of disseminated herpetic infection. Consider the risks and benefits of treatment before administering Imlygic to immunocompromised patients. Herpetic infections (including but not limited to cold sores and herpes keratitis) and serious cases of disseminated herpetic infections have been reported in patients treated with Imlygic (see SmPC section 4.8). For more information, please refer to the Summary of Product Characteristics.
II/0054	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2022		SmPC and PL	The SmPC section 6.6. has been updated as follows: Before use, thaw frozen Imlygic vials at room temperature (20°C to 25°C) until Imlygic is liquid. The time to achieve complete vial thaw is expected to be 30 to 70 minutes, depending on the ambient temperature. The PL have been updated accordingly.
IB/0055	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/07/2022	n/a		
II/0053	B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	21/07/2022	n/a		
II/0051	C.I.13 - Other variations not specifically covered	21/07/2022	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0052/G	This was an application for a group of variations. B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	23/06/2022	n/a		
PSUSA/10459 /202110	Periodic Safety Update EU Single assessment - talimogene laherparepvec	10/06/2022	n/a		PRAC Recommendation - maintenance
II/0050	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	19/05/2022	n/a		
II/0048	Update of section 4.4 of the SmPC in order to add a new warning about the potential risk of hepatic hemorrhage with the transcutaneous intrahepatic route of administration of talimogene laherparepvec.	24/03/2022	14/10/2022	SmPC and PL	SmPC new text: Imlygic is not indicated for transcutaneous intrahepatic route of administration. In clinical studies, cases of hepatic haemorrhage resulting in hospitalisation and death have

	In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				been reported in patients receiving transcutaneous intrahepatic Imlygic injections. For more information, please refer to the Summary of Product Characteristics.
II/0047/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	11/11/2021	14/10/2022	Annex II	The Annex II has been updated to include the IDT Biologika GmbH as active substance manufacturing site.
II/0046	Submission to provide preliminary efficacy results from the phase III part of the Study 20110265 to fulfil the obligation listed in the Annex II of the Product Information. The concerned study is a Phase 1b/3, multicenter trial of talimogene laherparepvec	14/10/2021	14/10/2022	Annex II	

	in combination with pembrolizumab compared with placebo in combination with pembrolizumab for treatment of unresectable stage IIIB to IVM1c melanoma. The Annex II is updated accordingly. 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				
II/0044	Submission of the final report from study 20180099 listed as a category 3 study in the RMP. This is a cross-sectional survey to evaluate physician knowledge of safety messages included in the physician education booklet (PEB) for Imlygic. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/09/2021	n/a		
PSUSA/10459 /202010	Periodic Safety Update EU Single assessment - talimogene laherparepvec	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0045	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	07/04/2021	n/a		

IB/0042	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/03/2021	n/a		
II/0041/G	This was an application for a group of variations. 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.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS	25/02/2021	n/a		
R/0039	Renewal of the marketing authorisation.	17/09/2020	18/11/2020	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Imlygic in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0040	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/07/2020	n/a		
PSUSA/10459 /201910	Periodic Safety Update EU Single assessment - talimogene laherparepvec	14/05/2020	n/a		PRAC Recommendation - maintenance
II/0036	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch	30/04/2020	n/a		

	control/testing takes place and any of the test method at the site is a biol/immunol method				
II/0037	B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	27/02/2020	n/a		
II/0034	To update the RMP for Imlygic to version 7.0 in order to add 2 category 3 studies (Studies 20180062 and 20180099), as well as an internal evaluation of managed distribution process metrics, to evaluate the effectiveness of additional risk minimization measures (aRMM). 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	19/09/2019	n/a		
IB/0035	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/07/2019	17/07/2020	Annex II	
PSUSA/10459 /201810	Periodic Safety Update EU Single assessment - talimogene laherparepvec	16/05/2019	n/a		PRAC Recommendation - maintenance

IA/0033	A.7 - Administrative change - Deletion of manufacturing sites	10/05/2019	n/a		
IB/0032	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	02/04/2019	n/a		
II/0029	Update of section 5.2 of the SmPC in order to update the pharmacokinetic properties information based on the final results from study 20120324, a phase 2, multicenter, single-arm trial to evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. This submission fulfils MEA 006.1. The RMP is updated accordingly (final consolidated version 6.0). In addition, the Marketing authorisation holder (MAH) took the opportunity to update Annex II as per the already assessed EMEA/H/C/002771/ANX/001 procedure. In addition, the MAH took the opportunity to update the details of local representatives for Ireland and Portugal in the package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/03/2019	06/06/2019	SmPC, Annex II and PL	The biodistribution and shedding of intralesionally administered talimogene laherparepvec were investigated in a clinical study that measured talimogene laherparepvec DNA in blood, urine, injection site, exterior of the occlusive dressings, oral mucosa, anogenital area, and suspected herpetic lesions. Sixty patients with melanoma received Imlygic intralesional injection and talimogene laherparepvec DNA was present in all sites during the study. No samples had detectable talimogene laherparepvec DNA 30 days after the end of treatment in blood, urine, oral mucosa, and anogenital area and no samples had detectable talimogene laherparepvec DNA 60 days after end of treatment in injected lesions. Overall 3 of 19 patients with lesions of suspected herpetic origin had talimogene laherparepvec DNA present at any time during the study. No viral activity was detected in samples of the occlusive dressings, oral mucosa, anogenital area, and suspected herpetic lesions. Infectious talimogene laherparepvec virus was detected at the site of injection in 7 (11%) patients at multiple time points in the study; no samples were positive for viral infectivity after cycle 2 or after the end of treatment.
II/0028	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	28/03/2019	n/a		

	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				
IB/0031/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) 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	06/02/2019	n/a		
II/0027	Update of section 4.8 of the SmPC in order to add granulomatous dermatitis as new adverse drug reaction with an uncommon frequency and to update the adverse reaction dyspnoea from dyspnoea exertional to dyspnoea. The package leaflet has been aligned accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/12/2018	06/06/2019	SmPC and PL	
PSUSA/10459 /201804	Periodic Safety Update EU Single assessment - talimogene laherparepvec	29/11/2018	n/a		PRAC Recommendation - maintenance
II/0024	B.I.a.2.c - Changes in the manufacturing process of	20/09/2018	n/a		

	the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol				
IA/0026	A.7 - Administrative change - Deletion of manufacturing sites	13/09/2018	n/a		
PSUSA/10459 /201710	Periodic Safety Update EU Single assessment - talimogene laherparepvec	31/05/2018	30/07/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10459/201710.
IG/0946	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	04/06/2018	06/06/2019	PL	
II/0020	Update of section 4.8 of the SmPC in order to add the new ADR 'hypersensitivity' with a frequency allocation of 'unknown'. The Package Leaflet is updated accordingly. Further, the MAH is implementing a minor editorial change in section 3 of the SmPC in order to clarify that the current description of the liquid applies to both strengths, and minor changes in section 4.4 of the SmPC and the Package Leaflet regarding sorbitol and sodium subsequent to the revised Annex to the EC guideline on excipients in the labelling (EMA/CHMP/302620/2017). In addition, the MAH took the opportunity to update the contact details of the local representative in Slovenia in the Package	31/05/2018	30/07/2018	SmPC and PL	N/A

	Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0021/G	This was an application for a group of variations. B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	15/05/2018	30/07/2018	SmPC and PL	
IB/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	02/02/2018	n/a		
PSUSA/10459 /201704	Periodic Safety Update EU Single assessment - talimogene laherparepvec	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0017	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/11/2017	n/a		

IG/0853	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	10/11/2017	30/07/2018	Annex II and PL	
IB/0014/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	10/08/2017	n/a		
PSUSA/10459 /201610	Periodic Safety Update EU Single assessment - talimogene laherparepvec	05/05/2017	n/a		PRAC Recommendation - maintenance
IAIN/0013	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	26/04/2017	06/07/2017	SmPC and Labelling	
II/0008	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP -	21/04/2017	n/a		

	Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method				
IAIN/0012/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.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	31/03/2017	n/a		
IB/0011	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	03/03/2017	n/a		
PSUSA/10459 /201604	Periodic Safety Update EU Single assessment - talimogene laherparepvec	01/12/2016	n/a		PRAC Recommendation - maintenance
IB/0007	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	07/10/2016	n/a		
IA/0006	A.7 - Administrative change - Deletion of manufacturing sites	06/09/2016	n/a		
IB/0001/G	This was an application for a group of variations.	23/07/2016	06/07/2017	SmPC and PL	

	A.6 - Administrative change - Change in ATC Code/ATC Vet Code B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0003	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	15/06/2016	n/a		
IB/0002	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	15/06/2016	n/a		