PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Imlygic® (Talimogene Laherparepvec)

This is a summary of the risk management plan (RMP) for Imlygic. The RMP details important risks of Imlygic, how these risks can be minimized, and how more information will be obtained about Imlygic's risks and uncertainties (missing information).

Imlygic's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Imlygic should be used.

This summary of the RMP for Imlygic should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Imlygic's RMP.

I. The medicine and what it is used for

Imlygic is authorized for treatment of adults with unresectable (cannot be removed by surgery) melanoma (a kind of skin cancer) that is regionally (in the skin or lymph nodes near the original skin tumor) or distantly metastatic (spread to distant areas of skin or lymph nodes) (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral (internal organ) disease. It contains talimogene laherparepvec as the active substance and it is given by intralesional injection (injection into the tumor).

Further information about the evaluation of Imlygic's benefits can be found in Imlygic's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage: https://www.ema.europa.eu/medicines/human/EPAR/Imlygic.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Imlygic, together with measures to minimize such risks and the proposed studies for learning more about Imlygic's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimizes its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Imlygic, these measures are supplemented with *additional risk minimization measures* mentioned under relevant risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Imlygic is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Imlygic are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Imlygic. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risk	• Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) • Accidental exposure of healthcare provider to talimogene laherparepvec • Immune-mediated adverse reactions
Important Potential Risk	• Disseminated herpetic infection in immunocompromised patients (such as those with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents) • Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Combination with other therapies like chemotherapy or immunosuppressive agents • Talimogene laherparepvec-mediated anti-granulocyte macrophage colony stimulating factor antibody response
Missing Information	• Pregnant and lactating women • Pediatric patients • Long-term safety data • Long-term efficacy data • Treatment of patients with metastatic lesions greater than 3 cm

II.B. Summary of Important Risks

Important Identified Risk: Disseminated herpetic infection (herpes infection occurring throughout the body) in severely immunocompromised individuals (those with any severe congenital [present at birth] or acquired cellular and/or humoral immune deficiency [weakness of the immune system])	
Evidence for linking the risk to the medicine	This important identified risk was identified based on nonclinical data.
Risk factors and risk groups	Individuals with any severe congenital or acquired cellular and/or humoral immune deficiency.
Risk minimization measures	Routine risk measures: • SmPC Sections 4.3, 4.4, and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20180062 • Study 20180099 • Quantitative polymerase chain reaction (qPCR) testing for talimogene laherparepvec DNA (a laboratory test to detect the presence of talimogene laherparepvec DNA) See Section II.C of this summary for an overview of the postauthorization development plan

Important Identified Risk: Accidental exposure of healthcare provider to talimogene laherparepvec	
Evidence for linking the risk to the medicine	This risk was identified based on reports in the clinical study setting.
Risk factors and risk groups	Numerous factors, some modifiable and some not, place healthcare providers at an increased risk for accidental exposure such as sustaining a needle stick injury. These factors include occupation, training, proper disposal of sharps, and medical activity being performed (National Institute for Occupational Safety and Health, DHHS (NIOSH), 1999; Publication No. 2000-2108).
Risk minimization measures	Routine risk communication: • SmPC Sections 4.2, 4.4, and 6.6 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet •
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20180099 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Identified Risk: Immune-mediated adverse reactions	
Evidence for linking the risk to the medicine	This is considered an important identified risk based on reports in the clinical study setting.
Risk factors and risk groups	Risk factors for an immune-mediated adverse reaction include host factors (eg, demographics, other comorbidities), host genotypes (Thong and Tan, *Br J Clin Pharmacol,* 2011; 71:684-700), and pre-existing autoimmune disease.
Risk minimization measures	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Additional risk minimization measures: None

Important Potential Risk: Disseminated herpetic infection (herpes infection occurring throughout the body) in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents)	
Evidence for linking the risk to the medicine	This risk is considered an important potential risk based on nonclinical data.
Risk factors and risk groups	Immunosuppression can be due to congenital immunodeficiency, acquired disease (HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, generalized malignancy), pharmacotherapy (immunosuppressive agents, radiation, or large amounts of corticosteroids), or extremes of age (neonates and elderly) (Chinen and Shearer, *J Allergy Clin Immunol*, 2010; 125(suppl 2):195-203; Notarangelo, *J Allergy Clin Immunol*, 2010; 125(suppl 2):182-194). The precise risk factors applicable to this risk with talimogene laherparepvec are unknown.
Risk minimization measures	Routine risk communication: • SmPC Sections 4.4 and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20180062 • Study 20180099 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Potential Risk: Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation)	
Evidence for linking the risk to the medicine	This risk is considered an important potential risk based on clinical and nonclinical data.
Risk factors and risk groups	Direct contact with injected lesions, protective dressings, or body fluids of treated patients. The likelihood of transfer of talimogene laherparepvec to a close contact or healthcare provider increases if the contact has a break in the skin or mucous membranes.
Risk minimization measures	Routine risk communication: • SmPC Sections 4.4 and 6.6 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20180062 • Study 20180099 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Potential Risk: Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients	
Evidence for linking the risk to the medicine	This risk is considered an important potential risk based on clinical data.
Risk factors and risk groups	No risk factors have been identified.
Risk minimization measures	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20180062 • Study 20180099 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Potential Risk: Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients	
Evidence for linking the risk to the medicine	This risk is considered an important potential risk based on nonclinical data.
Risk factors and risk groups	Previous infection with wild-type herpes simplex virus type 1. Fever, stress, and other factors are common triggers of recurrence.
Risk minimization measures	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20180062 • Study 20180099 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Potential Risk: Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection	
Evidence for linking the risk to the medicine	This important potential risk was identified based on theoretical concern and limited data with immunocompromised patients treated with talimogene laherparepvec.
Risk factors and risk groups	Immunosuppression can be due to congenital immunodeficiency, acquired disease (HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, generalized malignancy), pharmacotherapy (immunosuppressive agents, radiation or large amounts of corticosteroids), or extremes of age (neonates and elderly) (Chinen and Shearer, *J Allergy Clin Immunol*, 2010; 125(suppl 2):195-203; Notarangelo, *J Allergy Clin Immunol*, 2010; 125(suppl 2):182-194). The precise risk factors applicable to this risk with talimogene laherparepvec are unknown.
Risk minimization measures	Routine risk communication: • SmPC Sections 4.3, 4.4, and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet •
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20180099 • qPCR testing for talimogene laherparepvec DNA See Section II.C of this summary for an overview of the postauthorization development plan

Important Potential Risk: Combination with other therapies like chemotherapy or immunosuppressive agents	
Evidence for linking the risk to the medicine	This is considered an important potential risk based on nonclinical data from immunocompromised mice.
Risk factors and risk groups	Patients receiving concomitant chemotherapeutic or immunosuppressive therapies.
Risk minimization measures	Routine risk communication: • SmPC Section 4.4 • PL Section 2

Important Potential Risk: Talimogene laherparepvec-mediated anti-granulocyte macrophage colony stimulating factor antibody response (development of antibodies to granulocyte macrophage colony stimulating factor, which is a chemical in the body that increases the production of white blood cells)	
Evidence for linking the risk to the medicine	This risk is considered an important potential risk based on theoretical concerns.
Risk factors and risk groups	Risk factors are unknown for the development of antibodies against granulocyte macrophage colony stimulating factor (Meager et al, *Immunology*, 1999; 97:526-532).
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Testing of anti-granulocyte macrophage colony stimulating factor antibodies See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Pregnant and lactating women	
Risk minimization measures	Routine risk communication: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 Additional risk minimization measures: • Managed Distribution Program • Physician Education Booklet • Patient Safety Brochure • Patient Alert Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20180062 • Study 20180099 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Pediatric patients	
Risk minimization measures	Routine risk communication: • SmPC Section 4.2 • PL Section none Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20110261 • Study to be determined See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Long-term safety data	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20120139 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Long-term efficacy data	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study 20130193 • Study 20120139 See Section II.C of this summary for an overview of the postauthorization development plan

Missing Information: Treatment of patients with metastatic lesions greater than 3 cm	
Risk minimization measures	No risk minimization measures

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study Short Name	Purpose of the Study
Study 20110265 A phase 1b/3, multicenter trial of talimogene laherparepvec in combination with pembrolizumab (MK-3475) for treatment of unresectable, stage IIIB to IVM1c melanoma	Primary Objectives • Phase 1b: To evaluate the safety, as assessed by incidence of dose-limiting toxicity, of talimogene laherparepvec in combination with pembrolizumab in subjects with previously untreated, unresectable, stage IIIB to IVM1c melanoma. • Phase 3: To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by progression-free survival (response evaluation by blinded independent central review using modified Response Evaluation Criteria in Solid Tumors 1.1 [RECIST]) and overall survival. Efficacy uncertainties addressed: Preliminary efficacy
Study 20110266 A phase 2, multicenter, randomized, open-label trial assessing the efficacy and safety of talimogene laherparepvec neoadjuvant treatment plus surgery versus surgery alone for resectable, stage IIIB to IVM1a melanoma	Primary Objective To estimate the treatment effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on recurrence-free survival. Efficacy uncertainties addressed: Preliminary efficacy and safety

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Study 20130193 A postmarketing prospective cohort study of melanoma patients treated with IMLYGIC® (talimogene laherparepvec) in clinical practice to characterize the risk of herpetic infection among patients, close contacts, and health care providers; and long-term safety in treated patients.	Estimate the incidence rate of herpetic infection detection of talimogene laherparepvec DNA among patients for up to 5 years after the first IMLYGIC dose. Safety concerns addressed: • Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) • Accidental exposure of healthcare provider to talimogene laherparepvec • Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents) • Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Long-term safety data • Long-term efficacy data
Study 20110261 A phase 1 multi-center, open label, dose de-escalation study to evaluate the safety and efficacy of talimogene laherparepvec in pediatric subjects with advanced non-central nervous system (outside brain and spinal cord) tumors that are amenable to direct injection.	To evaluate the safety and tolerability of talimogene laherparepvec as assessed by incidence of dose-limiting toxicities, in pediatric subjects with advanced non-central nervous system tumors that are amenable to direct injection. Safety concerns addressed: Pediatric patients

Study Short Name	Purpose of the Study
Study 20120139 A registry study to evaluate the survival and long-term safety and subjects who previously received talimogene laherparepvec in Amgen or BioVEX-sponsored clinical trials	• To evaluate the long-term safety of talimogene laherparepvec • To monitor the subject overall survival <u>Safety concerns addressed:</u> • Long-term safety data • Long-term efficacy data
Study to be determined A randomized, controlled study to evaluate the safety and efficacy of talimogene laherparepvec in children from birth to < 18 years of age with a pediatric solid malignant tumor as part of a multi-modal treatment approach	To be determined <u>Safety concerns addressed:</u> Pediatric patients
Study 20180062 A cross-sectional survey to evaluate patient knowledge of safety messages included in the Patient Safety Brochure and Patient Alert Card for IMLYGIC®	Primary Objective To evaluate patients' knowledge levels of the key messages included in the IMLYGIC Patient Safety Brochure among patients who receive IMLYGIC. Secondary Objective To evaluate patients' levels of receipt and reading of the IMLYGIC Patient Safety Brochure and receipt, reading, and use (ie, carrying) of the Patient Alert Card among patients who receive IMLYGIC. Patients' understanding of the purpose of the Patient Alert Card will also be assessed. Safety concerns addressed • Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) • Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents) • Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients • Pregnant and lactating women

Study Short Name	Purpose of the Study
Study 20180099 A cross-sectional survey to evaluate physician knowledge of safety messages included in the Physician Education Booklet (PEB) for IMLYGIC®	<u>Primary Objective</u> To evaluate physicians' knowledge levels of the key messages included in the IMLYGIC Physician Education Booklet among physicians who completed the required IMLYGIC training. <u>Secondary Objectives</u> • To evaluate physicians' levels of receipt and reading of the IMLYGIC Physician Education Booklet among physicians who completed the required IMLYGIC training. • To evaluate physicians' understanding of the requirements to distribute the Patient Safety Brochure and Patient Alert Card. <u>Safety concerns addressed</u> • Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) • Accidental exposure of healthcare provider to talimogene laherparepvec • Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents) • Transmission of talimogene laherparepvec from patient to close contacts or healthcare providers via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type herpes simplex virus type 1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Pregnant and lactating women