EMA/713818/2015

Summary of the risk management plan (RMP) for Imlygic (talimogene laherparepvec)

This is a summary of the risk management plan (RMP) for Imlygic, which details the measures to be taken in order to ensure that Imlygic is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Imlygic, which can be found on Imlygic's EPAR page.

Overview of disease epidemiology

Imlygic is a medicine used for the treatment of adult patients with inoperable melanoma (a type of skin cancer) that has spread to other parts of the body (but not to bone, brain, lung or other internal organs).

The number of people diagnosed with melanoma is increasing worldwide. Melanoma accounts for less than 5% of skin cancer cases; however, it causes most skin cancer deaths. Ultraviolet light, white ethnicity, and advanced age are the main risk factors for melanoma.

In 2012, around 82,750 new melanomas occurred in 28 European countries. In about 6 out of 100 newly-diagnosed cases, the melanoma is inoperable or has metastasised (spread).

Summary of treatment benefits

Imlygic is a type of advanced therapy medicine called a 'gene therapy product'. This is a type of medicine that works by delivering genes into the body. Imlygic is injected inside the melanoma tumours. It contains the active substance talimogene laherparepvec, which is derived from a weakened virus (herpes simplex virus 1, the cold sore virus). This virus has been modified so it can infect and multiply inside melanoma cells, and also produce GM-CSF, a protein that stimulates the patient's immune system (the body's natural defences) to recognise and destroy melanoma cells.

Imlygic has been studied in one main study involving 436 patients with inoperable melanoma that had spread to other parts of the body (but not to bone and brain). The study, which lasted 24 months, compared Imlygic with GM-CSF injected under the skin. The main measure of effectiveness was the proportion of patients who responded to treatment and for whom the response lasted for at least six months before the patients' health declined or they required another therapy. Response to treatment was defined as reduction by at least 50% in the signs of melanoma.

When looking at the subset of patients in the study (249 patients) whose disease had not spread to the lung or other internal organs, 25% (41 out of 163) of patients treated with Imlygic had a sustained response to treatment, compared with around 1% (1 out of 86) of patients treated with GM-CSF.

Unknowns relating to treatment benefits

For the following patient groups no or only limited data are available:

- Pregnant or breastfeeding women
- Infants, children and adolescents
- Patients below 40 years of age
- Patients with kidney or liver problems (renal or hepatic impairment)
- Patients with heart problems (cardiac impairment)
- Patients of race or ethnic origin other than white
- Patients with cancer that has spread to the bones or to the brain (bone or cerebral metastases)
- Patients with cancer that has spread to more than 3 areas inside internal organs, such as heart, lungs, liver or intestines (more than 3 visceral lesions)
- Patients with cancer that has spread to other parts of the body and grown larger than 3 cm (metastatic lesions greater than 3 cm)
- Patients with melanoma of the eye (ocular melanoma)
- Patients with melanoma of the membrane that lines internal cavities of the body, such as nose, mouth, anus and vagina (mucosal melanoma)

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Herpes infection which affects the entire body (disseminated herpetic infection) in patients with a severely impaired immune system (i.e. those with any severe congenital or acquired cellular and/or humoral immune deficiency)	There are no available data in people with impaired immune systems since they were not included in clinical trials with Imlygic. However, studies in mice with severely impaired immune systems show that they developed disseminated infection and died after receiving Imlygic.	The body's natural immune defenses are important to prevent Imlygic from spreading throughout the body. Patients who are severely immunocompromised must not be treated with Imlygic.
Accidental exposure of healthcare professionals to Imlygic	Healthcare professionals may be exposed to Imlygic during its preparation or administration.	All professionals handling Imlygic or material contaminated with Imlygic (including protective dressings) or administering injections must observe safety precautions (e.g. wear a protective gown or laboratory coat, safety glasses, and gloves). Healthcare professionals who

Risk	What is known	Preventability
		have a suppressed immune system or who are pregnant should not administer Imlygic and should not come into direct contact with the Imlygic injection site or body fluids of treated patients. In the event of accidental contact, exposed individuals should clean the affected areas with soap and water. If signs or symptoms of herpes infection develop, they should contact their healthcare professional.
Decreased airflow to the lungs (obstructive airway disorder)	Obstructive airway disorder has been reported following treatment with Imlygic.	Caution should be used when injecting Imlygic into melanomas close to major airways.
Immune-mediated adverse reactions	In clinical studies, approximately 2% of patients taking Imlygic reported immune-mediated adverse reactions including kidney disease (glomerulonephritis), narrowing or blockage of blood vessels (vasculitis), swelling of the lungs (pneumonitis), and worsening psoriasis. It is not clear how Imlygic treatment caused these events.	The risks and benefits of Imlygic should be considered before starting treatment in patients who have autoimmune diseases or before continuing treatment in patients who develop immune-mediated adverse reactions.
Lump containing white blood cells (plasmacytoma) at the injection site	In the main clinical study plasmacytoma in the area where Imlygic had been injected was reported in 1 patient. This patient also had a blood disorder called multiple myeloma.	The risks and benefits of Imlygic should be considered in patients with multiple myeloma or in whom plasmacytoma develops during treatment.
Blood clot in one of the deep veins in the body (deep vein thrombosis)	Deep vein thrombosis has been reported in up to 1 in 10 patients receiving Imlygic.	No specific preventive measures are recommended.
Infection of the deep layers of the skin (cellulitis) at the site of injection	Cellulitis at injection sites has been reported in 2.1% of patients receiving Imlygic. Blood poisoning (bacterial sepsis) was reported in some cases and hospitalisation was required for treatment with intravenous (into a vein) antibiotics.	Careful wound care and infection precautions are recommended.

Important potential risks

Risk	What is known
Herpes infection affecting the entire body (disseminated herpetic infection) in individuals who have problems with their immune system (i.e. those with HIV/AIDS, leukaemia, lymphoma, common variable immunodeficiency, or those who require high-dose of steroids or other immunosuppressive medicines)	There are no available data on people with impaired immune systems since they were not included in clinical trials with Imlygic. However, mice with severely impaired immune systems developed widespread infection and died after receiving Imlygic. It is possible that people with cancer, HIV/AIDS, or people who take medications to suppress the immune system (such as corticosteroids) are at an increased risk for developing serious or life-threatening infections after receiving Imlygic. The risks and benefits of treatment with Imlygic should be considered before giving Imlygic to patients who have problems with their immune system.
Spread of Imlygic to close contacts or healthcare providers after direct contact with injected lesions or body fluids	Imlygic could be spread to a patient's close contacts (household members, caregivers, sex partners, or someone a patient shares a bed with) after the patient's tumour is injected with Imlygic. This may occur following direct contact with a patient's body fluids or injection sites. In animals treated with Imlygic, the product was found in body tissues up to 12 weeks after injection. In patients treated with Imlygic in clinical trials, the virus in Imlygic has been found on the surface of the injected tumours, within the first few hours and up to 7 days after the injection, although it is not known exactly for how long it may be present. Imlygic has not been detected on the outside of the dressing that is placed on top of the injected melanoma lesions in patients in clinical trials.
Spread of Imlygic to other parts of the body, which could cause an oral herpes infection like cold sores	Since Imlygic contains a virus, there is a concern that Imlygic could potentially spread beyond the tumour site to other parts of the body and cause an infection in normal (non-cancer) cells. This has not been seen in the clinical studies or in animal studies with Imlygic.
Symptomatic herpes infection due to latency and reactivation of either Imlygic's virus or of the herpes virus in patients who previously were infected with the naturally occurring virus	Patients who have had a previous herpes infection may have inactive (latent) herpes simplex virus within their body. Taking Imlygic may activate this latent virus and could cause infection. Also, there is the potential for patients who have been treated with Imlygic to have inactive (latent) Imlygic virus within their body, which could become active and cause a infection. In clinical studies, 5.5% of patients taking Imlygic experienced signs of herpes infection.
Patients with a weakened immune system (immunocompromised patients) treated with Imlygic and suffering simultaneoulsy from another infection	There are no available data on people with impaired immune systems since they were not included in clinical trials with Imlygic. However, mice with severely impaired immune systems developed widespread infection and died after receiving Imlygic. It is possible that people with cancer, HIV/AIDS, people who take medications to suppress the immune system (such as corticosteroids) could be at increased risk for developing serious or life-threatening infections after receiving Imlygic.
Patients taking Imlygic in	There are no available data on people with impaired immune systems

Risk	What is known
combination with other therapies like chemotherapy or immunosuppressive agents	since they were not included in clinical trials with Imlygic. However, mice with severely impaired immune systems developed widespread infection and died after receiving Imlygic. People with cancer, HIV/AIDS, or people who take medications to suppress the immune system (such as corticosteroids) could be at increased risk for developing serious or life-threatening infections after receiving Imlygic.
Combining (recombination) Imlygic's virus with herpes (wild-type herpes simplex virus -1)	The likelihood of the virus in Imlygic combining with the naturally occurring herpes simplex virus -1 is low.
Impaired wound healing at site of injection	Delayed wound healing at or around the injection site may occur after receiving Imlygic. This is more likely in patients who have previously been treated with radiation at the injection site. One patient in the main clinical study experienced delayed wound healing at the injection site on the lower leg several months after treatment with Imlygic. This resulted in an amputation below the knee. However, this patient had other medical conditions that could have contributed to the occurrence of this event.
Delayed initiation of subsequent treatment for melanoma with other melanoma medicines in patients who do not respond to treatment with Imlygic (non-responders)	When Imlygic replicates (reproduces), it produces a protein known as GM-CSF, which increases the numbers of white blood cells to produce an immune response. Theoretically, this response could be delayed, which could delay Imlygic from working. Therefore, differentiation between delayed response and no response to treatment with Imlygic will be difficult, which would delay subsequent treatment.
Loss of effectiveness (efficacy) in patients treated with aciclovir by mouth or injection (systemic aciclovir) for complications	Herpes simplex virus-1 (commonly called the cold sore virus) can be treated with acyclovir by mouth or injection (systemic acyclovir) in patients with complications arising from this virus. Imlygic is a modified herpes virus and so theoretically acyclovir could stop Imlygic from working.
Immune response against GM-CSF	When the virus in Imlygic replicates (reproduces), it produces a protein known as GM-CSF, which stimulates the immune system to kill melanoma cells. Theoretically, the body could produce an immune response to GM-CSF. It is not known whether this is something that could be expected with treatment with Imlygic.

Missing information

Risk	What is known
Limited information on how Imlygic is distributed throughout the body and removed (shed) from the body in	Limited information is available regarding how Imlygic is distributed throughout the body and removed from the body.

Risk	What is known
patients with melanoma	
Pregnant or breastfeeding women	Imlygic has not been studied in women who are pregnant or breastfeeding. In a study in animals in which very high doses of Imlygic were given during pregnancy, there were no effects on the development of the offspring. If a pregnant woman is infected with herpes simplex virus, there is potential for the virus to cross the placental barrier. Herpes virus infection also poses a risk to the baby becoming infected during birth. These infections have been associated with serious adverse effects, including multi-organ failure and death, if a fetus or neonate contracts the herpes infection. It is unknown whether Imlygic would act in the same manner as herpes simplex virus.
Infants, children and adolescents	Imlygic has not been studied in patients under 18 years of age and it is therefore not known whether Imlygic is safe and effective in these patients. However, 2 clinical studies are planned in children aged from birth to 18 years. Study 20110261 will include children with melanoma or with advanced solid tumours, excluding cancer of the brain or spinal cord (central nervous system), for which no effective treatment is known. A second study will include children with solid tumors who will receive Imlygic as well as other types of treatment.
Patients below 40 years of age	Limited information is available regarding the use of Imlygic in patients below 40 years, since most patients who took part in clinical trials were aged between 50 and 80 years.
Patients with kidney or liver problems (renal or hepatic impairment)	Imlygic has not been studied in patients with severe kidney or liver problems.
Patients with heart problems (cardiac impairment)	Imlygic has not been studied in patients with heart problems.
Patients of race or ethnic origin other than white	Most patients studied in clinical trials so far have been white. Therefore, information in patients of other race or ethnic origin is limited.
Long-term safety data	Long-term safety of treatment with Imlygic has not yet been fully studied, although available information that has been gathered thus far has not identified any long-term safety concerns.
Long-term efficacy data	Long-term efficacy of treatment with Imlygic has not yet been fully studied, although available information that has been gathered thus far has not identified any long-term efficacy concerns.
Patients with cancer that has spread to the bones (bone metastases)	Imlygic has not been studied in patients with cancer that has spread to the bones.
Patients with cancer that has spread to the brain (cerebral metastases)	Imlygic has not been studied in patients with cancer that has spread to the brain.
Treatment of patients	Imlygic has not been studied in patients with cancer that has spread to more

Risk	What is known
with cancer that has spread to more than 3 areas inside internal organs, such as heart, lungs, liver, or intestines (more than 3 visceral lesions)	than 3 separate areas inside internal organs, such as heart, lungs, liver or intestines.
Patients with cancer that has spread to other parts of the body and grown larger than 3 cm (metastatic lesions greater than 3 cm)	Imlygic has not been studied in patients with cancer that has spread to other parts of the body and grown larger than 3 cm.
Patients with melanoma of the eye (ocular melanoma)	Imlygic has not been studied in patients with melanoma of the eye.
Patients with melanoma of the membrane that lines internal cavities of the body, such as nose, mouth, anus, and vagina (mucosal melanoma)	Imlygic has not been studied in patients with melanoma of the membrane that lines internal cavities of the body, such as nose, mouth, anus and vagina.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Imlygic can be found on Imlygic's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Imlygic's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Cold chain disruption / Herpes virus infection / Accidental exposure

Risk minimisation measure: Controlled distribution program / Educational material (physician booklet, patient brochure, patient alert card)

Description:

The controlled distribution programme is aimed at managing the product supply chain to ensure that cold storage requirements are observed and at controlling the distribution of Imlygic to qualified centers and up to the patients.

The Physician education booklets are provided to healthcare providers to inform about important risks.

Patient safety brochures are provided to prescribing physicians for distribution to patients receiving Imlygic. These provide important safety information for patients, including information patients can share with family, caregivers, and close contacts, and information on the risks of transmission of Imlygic, herpes infection, and serious infection in immunocompromised individuals.

Patient alert cards are provided to prescribing physicians for distribution to patients receiving Imlygic. This card is intended for the patient to present to healthcare providers upon consultation or hospitalisation and informs that the holder has been treated with Imlygic. The card refers the reader to product labeling, and provides contact details for further information.

The following important risks associated with Imlygic are addressed in the educational material:

- Herpetic infection occurring throughout the entire body (disseminated herpetic infection) in severely immunocompromised individuals
- Herpetic infection occurring throughout the entire body (disseminated herpetic infection) in individuals who have problems with their immune system (ie, HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents)
- Accidental exposure of healthcare providers to Imlygic
- Spread of Imlygic to close contacts or healthcare providers after direct contact with injected lesions or body fluids
- Spread of Imlygic to other parts of the body, which could cause herpes infection, like cold sores
- Symptomatic herpetic infection due to latency and reactivation of Imlygic or herpes (wild-type HSV-1) in patients
- Patients with a weakened immune system (immunocompromised patients) treated with Imlygic and suffering from concomitant infection
- Combination with other therapies like chemotherapy or immunosuppressive agents
- Exposure of pregnant and breastfeeding women

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study 20120139 A registry study to evaluate the survival and long-term safety of subjects with melanoma who previously received talimogene laherparepvec	- To evaluate the long-term safety of Imlygic - To monitor overall survival of patients treated with Imlygic	- Long-term safety data - Long-term efficacy data	Ongoing	Final study report anticipated July 2023
Study 20130193 A post-marketing, prospective cohort study of patients treated with talimogene laherparepvec in clinical practice to characterize the risk of herpetic illness among patients, close contacts, and healthcare providers; and long-term safety in treated patients	- To estimate the incidence rate of herpes containing talimogene laherparepvec's DNA among patients for 5 years after initiating Imlygic treatment - To estimate the proportion of patients having herpes containing talimogene laherparepvec's DNA within 6 months of initiating Imlygic's treatment - To estimate the rate of herpes manifestations (eg, keratitis, encephalitis, disseminated infection) among immunocompromised patients receiving Imlygic	- Herpes infection occurring throughout the entire body (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 - Herpes infection occurring throughout the entire body (disseminated herpetic infection) in individuals who have problems with their immune system (ie, HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents)	Planned	Periodic regulatory reports; Final study report anticipated February 2025

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study 20130193 A post-marketing, prospective cohort study of patients treated with talimogene laherparepvec in clinical practice to characterize the risk of herpetic illness among patients, close contacts, and healthcare providers; and long-term safety in treated patients (continued)	- To estimate the rate of herpes lesions containing talimogene laherparepvec's DNA among patients after ending use of Imlygic (ie, symptomatic reactivation) - To count the number of close contacts and healthcare providers having a herpes containing Imlygic's DNA - To characterize herpes manifestations (eg, keratitis, encephalitis, disseminated infection) among close contacts and healthcare providers - To characterize adverse drug reactions and serious adverse drug reactions among patients receiving Imlygic - To describe the demographics, disease characteristics, and treatment use among patients receiving Imlygic in real world, clinical practice - To characterize overall survival of patients receiving talimogene laherparepvec in real world, clinical practice	- Spread of Imlygic to close contacts or healthcare providers after direct contact with injected melanomas or body fluids - Spread of Imlygic to other parts of the body, which could cause infection and/or sores, like cold sores - Symptomatic herpetic infection due to latency and reactivation of Imlygic or herpes (wild-type HSV-1) in patients -Immunocompromised patients treated with Imlygic and suffering from concomitant infection - Combination with other therapies like chemotherapy or immunosuppressive agents - Long-term safety data - Long-term efficacy data		
Study 20120324 A phase 2, multicenter, single-arm trial to	-To estimate the proportion of subjects with detectable Imlygic's DNA in the	- Accidental exposure of HCP to Imlygic - Spread of Imlygic to close contacts or	Ongoing in US	Primary analysis clinical study report anticipated

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
evaluate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma	blood and urine any time after administration of Imlygic's within the first 3 cycles - To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine overall and by baseline HSV-1 status (seronegative versus seropositive) during each of the first 3 cycles - To estimate the rate of detection and subject incidence of Imlygic's DNA and virus from exterior of occlusive dressing and injected lesion - To estimate the rate of detection and subject incidence of Imlygic's DNA and virus in oral mucosa swabs during treatment and after end of treatment - To estimate the rate of detection and subject incidence of talimogene laherparepvec DNA in genital swabs during treatment and after end of treatment for subjects injected with talimogene laherparepvec below the waist - To estimate the incidence of detection of talimogene	healthcare providers after direct contact with injected lesions or body fluids - Spread of Imlygic to other parts of the body, which could cause infection and/or sores, like cold sores - Symptomatic herpes infection due to latency and reactivation of Imlygic or herpes (wild-type HSV-1) in patients - Additional information on how Imlygic is distributed throughout the body and shed from the body in patients with melanoma		August 2016; Final analysis clinical study report anticipated February 2017

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	laherparepvec DNA in lesions suspected to be herpetic in origin - To describe the efficacy of talimogene laherparepvec as assessed by objective response rate, as well as by best overall response rate, duration of response, and durable response rate achieved in subjects with unresected, stage IIIB-IVM1c melanoma - To describe the safety profile of talimogene laherparepvec in subjects with unresected, stage IIIB-IVM1c melanoma			
Study 20110261 Phase 1, open-label, dose de-escalation study to evaluate the tolerability, safety, and activity of talimogene laherparepvec in children from birth to < 18 years of age with melanoma or with advanced non-CNS tumors that are amenable to direct injection and for which no effective treatment is known	- To be determined	- Safety in children	Planned	To be determined
Study Number:	- To be determined	Safety in children	Planned	To be

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
To be determined 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				determined

Studies which are a condition of the marketing authorisation

The three studies below are a condition of the marketing authorisation:

Description	Due date
Study 20120325: the company should submit the preliminary results of Study 20120325 (a phase 2, multicenter, open-label, single-arm trial to evaluate the correlation between objective response rate and baseline intratumoral CD8+T-lymphocyte density in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec)	31st December 2018
Study 20110266: the company should submit the preliminary results from Study 20110266 (a phase 2, multicenter, randomized, open-label trial assessing the efficacy and safety of talimogene laherparepvec neoadjuvant treatment plus surgery vs surgery alone for resectable stage IIIB to IVM1a melanoma).	31th December 2019
Study 20110265: the company should provide preliminary efficacy results from the phase III part of the Study 20110265 (a multicenter trial evaluating the combination of talimogene laherparepvec with pembrolizumab).	30th June, 2019

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 12-2015.