Revised in December 2020.

1. NAME OF THE MEDICINAL PRODUCT

Imlygic 10^6 plaque forming units (PFU)/mL solution for injection
Imlygic 10^8 plaque forming units (PFU)/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Talimogene laherparepvec is an attenuated herpes simplex virus type-1 (HSV-1) derived by functional deletion of 2 genes **(**ICP34.5 and ICP47) and insertion of coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF) (see section 5.1).

Talimogene laherparepvec is produced in Vero cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Imlygic 10^6 plaque forming units (PFU)/mL solution for injection

Each vial contains 1 mL deliverable volume of Imlygic at a nominal concentration of 1×10^6 (1 million) plaque forming units (PFU)/mL.

Imlygic 10^8 plaque forming units (PFU)/mL solution for injection

Each vial contains 1 mL deliverable volume of Imlygic at a nominal concentration of 1×10^8 (100 million) plaque forming units (PFU)/mL.

Excipient with known effect

Each 1 mL vial contains 7.7 mg sodium and 20 mg sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Imlygic 10^6 plaque forming units (PFU)/mL solution for injection

Clear to semi-translucent liquid following thaw from its frozen state.

It may contain white, visible, variously shaped, virus-containing particles.

Imlygic 10^8 plaque forming units (PFU)/mL solution for injection

Semi-translucent to opaque liquid following thaw from its frozen state.

It may contain white, visible, variously shaped, virus-containing particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imlygic is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease (see sections 4.4 and 5.1).

4.2 Posology and method of administration

Treatment with talimogene laherparepvec should be initiated and supervised by a qualified physician experienced in the treatment of cancer.

Patients treated with Imlygic must be given the Patient Alert Card and be informed about the risks of the treatment.

Posology

Imlygic is provided in single-use vials of 1 mL each in two different concentrations:
- 10^6 (1 million) PFU/mL - For initial dose only.
- 10^8 (100 million) PFU/mL - For all subsequent doses.

The total injection volume for each treatment visit should be up to a maximum of 4 mL. The initial recommended dose is up to a maximum of 4 mL of Imlygic at a concentration of 10^6 (1 million) PFU/mL. Subsequent doses should be administered up to 4 mL of Imlygic at a concentration of 10^8 (100 million) PFU/mL.

The recommended dosing schedule is shown in table 1.

Table 1: Recommended dosing schedule

Treatment visit	Treatment interval	Maximum total injection volume	Dose concentrations	Prioritization of lesions to be injected
Initial	-	Up to 4 mL	10^6 (1 million) PFU/mL	• Inject largest lesion(s) first. • Prioritize injection of remaining lesions based on lesion size until maximum injection volume is reached.
Second	3 weeks after initial treatment	Up to 4 mL	10^8 (100 million) PFU/mL	• First inject any new lesions (lesions that may have developed since initial treatment). • Prioritize injection of remaining lesions based on lesion size until maximum injection volume is reached.
All subsequent treatment visits (including re-initiation)	2 weeks after previous treatment	Up to 4 mL	10^8 (100 million) PFU/mL	• First inject any new lesions (lesions that may have developed since previous treatment). • Prioritize injection of remaining lesions based on

				lesion size until maximum injection volume is reached.

Determining Imlygic dose volume (per lesion)

The volume to be injected into each lesion is dependent on the size of the lesion and should be determined according to table 2. The total injection volume for each treatment session should be up to a maximum of 4 mL.

Table 2: Selection of Imlygic injection volume based on lesion size

Lesion size (longest dimension)	**Imlygic injection volume**
> 5 cm	up to 4 mL
> 2.5 cm to 5 cm	up to 2 mL
> 1.5 cm to 2.5 cm	up to 1 mL
> 0.5 cm to 1.5 cm	up to 0.5 mL
≤ 0.5 cm	up to 0.1 mL

Patients may experience increase in size of existing lesion(s) or the appearance of a new lesion prior to achieving a response. As long as there are injectable lesion(s) remaining, Imlygic should be continued for at least 6 months unless the physician considers that the patient is not benefitting from Imlygic treatment or that other treatment is required.

Imlygic treatment may be reinitiated if new lesions appear following a complete response and the physician considers that the patient will benefit from treatment.

Special populations

Elderly population

No adjustment of the dose is required in patients ≥ 65 years old (see section 5.1).

Hepatic and renal impairment

No clinical studies have been conducted to evaluate the effect of hepatic or renal impairment on the pharmacokinetics of talimogene laherparepvec. However, no adjustment in dosage is necessary for patients with hepatic or renal impairment.

Pediatric population

The safety and efficacy of Imlygic in pediatric patients has not been established. No data are available.

Method of administration

Imlygic is to be administered by intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance.

Precautions to be taken before manipulating or administering the medicinal product

This medicinal product contains genetically modified organisms. Personal protective equipment should be worn while preparing or administering talimogene laherparepvec (see section 6.6).

Healthcare professionals who are immunocompromised or pregnant should not administer Imlygic and should not come into direct contact with the injection site(s) or body fluids of treated patients (see sections 4.3 and 4.4).

Follow the instructions below to prepare and administer Imlygic to patients:

Pre-injection
- Thaw Imlygic vial(s) at room temperature. Thawed vials may be stored prior to administration (see section 6.3). For handling of thawed vials, see section 6.6.
- Draw the desired amount of Imlygic from the vial into a syringe using aseptic technique. A 22- to 26-gauge needle is recommended.
- The injection site may be treated with a topical anesthetic agent. Injectable anesthetic may be injected around the periphery of the lesion but should not be injected directly into the lesion.
- Clean the lesion and surrounding areas with an alcohol swab and let dry.

Injection
- Inject Imlygic intralesionally into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable or detectable by ultrasound guidance.
- Determine injection volume for each lesion using table 2 above.
- Using a single insertion point, inject Imlygic along multiple tracks as far as the radial reach of the needle allows within the lesion to achieve even and complete dispersion. Multiple insertion points may be used if a lesion is larger than the radial reach of the needle.

Cutaneous lesions

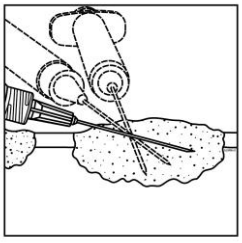


Figure 1:
Injection administration for cutaneous lesions

Subcutaneous lesions

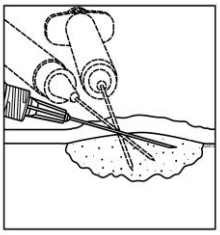


Figure 2:
Injection administration for subcutaneous lesions

Nodal lesions

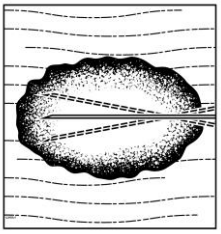


Figure 3:
Injection administration for nodal lesions

- Disperse Imlygic evenly and completely within the lesion by pulling the needle back without exiting the lesion. Redirect the needle as many times as necessary while injecting the remainder of the dose . Continue until the full dose is evenly and completely dispersed.
- When removing the needle, withdraw it from the lesion slowly to avoid leakage or splash-back of Imlygic at the insertion point.
- Repeat these steps for other lesions that need to be injected. Use a new needle anytime the needle is completely removed from a lesion and each time a different lesion is injected.

Post-injection
- Apply pressure to the injection site with a sterile gauze for at least 30 seconds.
- Swab the injection site and surrounding area with alcohol, and cover the injected lesion with an absorbent pad and dry occlusive dressing.

4.3 Contraindications

- Patients with a history of hypersensitivity to talimogene laherparepvec or any of its excipients.
- Patients who are severely immunocompromised (e.g. patients with severe congenital or acquired cellular and/or humoral immune deficiency) (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Previously treated patients

Efficacy data for Imlygic in the current second or later line treatment settings are limited.

Immunocompromised patients

Imlygic has not been studied in immunocompromised patients. Based on animal data, patients who are severely immunocompromised may be at an increased risk of disseminated herpetic infection and should not be treated with Imlygic (see sections 4.3 and 5.3). Disseminated herpetic infection may also occur in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or who require chronic high-dose steroids or other immunosuppressive agents). The risks and benefits of treatment should be considered before administering Imlygic to these patients.

Accidental exposure to Imlygic

Accidental exposure may lead to transmission of Imlygic and herpetic infection. Healthcare professionals and close contacts (e.g. household members, caregivers, sex partners or persons sharing the same bed) should avoid direct contact with injected lesions or body fluids of treated patients during the entirety of the treatment period and up to 30 days after the last treatment administration (see section 6.6). Accidental needle stick and splash-back have been reported in healthcare professionals during preparation and administration.

Close contacts who are pregnant or immunocompromised should not change the patient's dressing or clean their injection site. Pregnant women, neonates, and immunocompromised individuals should not be exposed to potentially contaminated materials.

Healthcare professionals should ensure that patients are able to comply with the requirement to cover injection sites with occlusive dressings (see section 6.6). Patients should also be advised to avoid touching or scratching injection sites as this could lead to inadvertent transfer of Imlygic to other areas of their body or to their close contacts.

Although it is not known if Imlygic could be transmitted through sexual contact, it is known that wild-type HSV-1 can be transmitted through sexual contact. Patients should be advised to use a latex condom during sexual contact to prevent possible transmission of Imlygic. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment (see section 4.6).

Caregivers should be advised to wear protective gloves when assisting patients in applying or changing occlusive dressings and to observe safety precautions for disposal of used dressings and cleaning materials (see section 6.6).

In the event of an accidental exposure to Imlygic, follow instructions in section 6.6. If signs or symptoms of herpetic infection develop, they should contact their healthcare professional. In case

suspected herpetic lesions occur, patients, close contacts or healthcare providers have the option of follow-up testing by the Marketing Authorization Holder for further characterization of the infection.

Herpetic infection in Imlygic-treated patients

In clinical studies, herpetic infections (including cold sores and herpes keratitis) have been reported in patients treated with Imlygic. Symptoms of a local or systemic infection possibly related to Imlygic are anticipated to be similar to symptoms caused by wild-type HSV-1 infections.

Individuals with wild-type HSV-1 infection are known to be at a lifelong risk for symptomatic herpetic infection due to reactivation of latent wild-type HSV-1. Symptomatic herpetic infection due to possible reactivation of Imlygic should be considered.

Patients who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmission.

Talimogene laherparepvec is sensitive to acyclovir. The risks and benefits of Imlygic treatment should be considered before administering acyclovir or other anti-viral agents indicated for management of herpetic infection. These agents may interfere with the effectiveness of the treatment if administered systemically or topically directly to the injection site.

Information on herpetic lesions is provided in the Patient Safety Information Card.

Cellulitis at the injection site

Necrosis or ulceration of tumor tissue may occur following Imlygic treatment. Cellulitis and systemic bacterial infection have been reported. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds.

Impaired healing at the injection site

In clinical studies, impaired healing at the injection site has been reported. Imlygic may increase the risk of impaired healing in patients with underlying risk factors (e.g. previous radiation at the injection site, or lesions in poorly vascularized areas).

The risks and benefits of Imlygic should be considered before continuing treatment if persistent infection or delayed healing develops.

Immune-mediated events

In clinical studies, immune-mediated events including as glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo have been reported in patients treated with Imlygic.

The risks and benefits of Imlygic should be considered before initiating treatment in patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events.

Plasmacytoma at injection site

Plasmacytoma has been reported in proximity to the injection site after administration of Imlygic. The risks and benefits of Imlygic should be considered in patients with multiple myeloma or in whom plasmacytoma develops during treatment.

Obstructive airway disorder

Obstructive airway disorder has been reported following Imlygic treatment. Caution should be used when injecting lesions close to major airways.

HSV-1 seronegative patients

Patients who were HSV-1 seronegative at baseline were reported to have a greater incidence of pyrexia, chills, and influenza-like illness compared with those who were HSV-1 seropositive at baseline, especially within the period of the first 6 treatments (see section 4.8).

All patients

This medicinal product contains 20 mg sorbitol per 1 mL vial. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

This medicinal product contains 7.7 mg sodium per 1 mL vial, equivalent to 0.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with Imlygic. Acyclovir and other anti-viral agents may interfere with the effectiveness of the treatment if administered systemically or topically directly to the injection site. Consider the risks and benefits of Imlygic treatment before administering acyclovir or other anti-viral agents indicated for management of herpetic infection.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment .

All patients should be advised to use a latex condom during sexual contact to prevent possible transmission of Imlygic (see section 4.4).

Pregnancy

Adequate and well controlled studies with talimogene laherparepvec have not been conducted in pregnant women.

If a pregnant woman has an infection with wild-type HSV-1 (primary or reactivation), there is potential for the virus to cross the placental barrier, and also a risk of transmission during birth due to viral shedding. Infections with wild-type HSV-1 have been associated with serious adverse effects, including multi-organ failure and death, if a fetus or neonate contracts the wild-type herpes infection. While there are no clinical data to date on talimogene laherparepvec infections in pregnant women, there could be a risk to the fetus or neonate if talimogene laherparepvec were to act in the same manner. No effects on embryo-fetal development have been observed in animal studies (see section 5.3). As a precautionary measure, it is preferable to avoid the use of talimogene laherparepvec during pregnancy.

Transplacental metastases of malignant melanoma can occur. Because talimogene laherparepvec is designed to enter and replicate in the tumor tissue, there could be a risk of fetal exposure to talimogene laherparepvec from tumor tissue that has crossed the placenta.

If Imlygic is used during pregnancy, or if the patient becomes pregnant while taking the medicinal product, the patient should be apprised of the potential hazards to the fetus and/or neonate.

Breast-feeding

It is unknown whether talimogene laherparepvec is transferred into human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Imlygic therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical studies have been performed to evaluate the effects of talimogene laherparepvec on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Talimogene laherparepvec may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as dizziness and confusional state (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that talimogene laherparepvec does not adversely affect them.

4.8 Undesirable effects

Summary of safety profile

The safety of Imlygic was evaluated in the pivotal study where 292 patients received at least 1 dose of Imlygic (see section 5.1). The median duration of exposure to Imlygic was 23 weeks (5.3 months). Twenty six (26) patients were exposed to Imlygic for at least one year.

The most commonly reported adverse reactions (≥ 25%) in Imlygic-treated patients were fatigue (50.3%), chills (48.6%), pyrexia (42.8%), nausea (35.6%), influenza-like illness (30.5%), and injection site pain (27.7%). Overall, ninety eight per cent (98%) of these adverse reactions reported were mild or moderate in severity. The most common grade 3 or higher adverse reaction was cellulitis (2.1%) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions were determined based on clinical trials in patients with melanoma treated with Imlygic compared to GM-CSF and post-marketing experience. Incidence of adverse reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions from clinical trials in patients with melanoma and post-marketing experience

Infections and infestations	
Common	Cellulitis*, Oral herpes
Uncommon	Incision site infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	Tumor pain, Infected neoplasm
Uncommon	Plasmacytoma at injection site*
Blood and lymphatic system disorders	
Very common	edema peripheral
Common	Anemia
Immune system disorders	
Common	Immune-mediated events[†]*
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Common	Dehydration

Nervous system disorders	
Very common	Headache
Common	Confusional state, Anxiety, Depression, Dizziness, Insomnia
Eye disorders	
Uncommon	Keratitis herpetic
Ear and labyrinth disorders	
Common	Ear pain
Cardiac disorders	
Common	Tachycardia
Vascular disorders	
Common	Deep vein thrombosis, Hypertension, Flushing
Respiratory, thoracic and mediastinal disorders	
Very common	Cough
Common	Dyspnea, Oropharyngeal pain, Upper respiratory tract infection
Uncommon	Obstructive airways disorder
Gastrointestinal disorders	
Very common	Vomiting, Diarrhea, Constipation, Nausea
Common	Abdominal pain, Abdominal discomfort
Skin and subcutaneous tissue disorders	
Common	Vitiligo, Rash, Dermatitis
Uncommon	Granulomatous dermatitis
Musculoskeletal and connective tissue disorders	
Very common	Myalgia, Arthralgia, Pain in extremity
Common	Back pain, Groin pain
General disorders and administration site conditions	
Very common	Influenza-like illness*, Pyrexia, Chills, Fatigue, Pain, Injection site reactions[§]
Common	Malaise, Axillary pain
Investigations	
Common	Weight decreased
Injury, poisoning and procedural complications	
Common	Wound complication, Wound secretion, Contusion, Procedural pain

[§] Injection site reactions include: very common term of injection site pain, common terms of injection site erythema, injection site hemorrhage, injection site swelling, injection site reaction, injection site inflammation, secretion discharge, injection site discharge, uncommon term of injection site warmth.
[†] Immune-mediated events include: uncommon terms of vasculitis, pneumonitis, worsening psoriasis and glomerulonephritis.
* See Description of selected adverse reactions.

Description of selected adverse reactions

Immune-mediated events

Immune-mediated events reported in the pivotal clinical study included a case of worsening psoriasis in a patient with a prior history of psoriasis, one case of pneumonitis in a patient with a prior history of autoimmune disease, one case of vasculitis, and two cases of glomerulonephritis of which one presented with acute renal failure.

Plasmacytoma

In clinical trials, one case of plasmacytoma at injection site was observed in a patient who was found to have multiple myeloma.

Cellulitis

In the pivotal clinical trial (study 005/05), events of cellulitis were recorded, some of them being considered as serious adverse events. However, none lead to permanent discontinuation of Imlygic

treatment. Careful wound care and infection precautions are recommended, particularly if tissue necrosis results in open wounds.

Influenza-like symptoms

90% of patients treated with Imlygic experienced influenza-like symptoms. Pyrexia, chills, and influenza-like illness, which can occur any time during treatment, generally resolved within 72 hours. These events were reported more frequently within the period of the first 6 treatments, particularly in patients who were HSV-1 negative at baseline.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

There is no clinical experience with overdose with Imlygic. Doses up to 4 mL at a concentration of 10^8 PFU/mL every 2 weeks have been administered in clinical trials with no evidence of dose limiting toxicity. The maximum dose that can be safely administered has not been determined. In the event of a suspected overdose or inadvertent intravenous administration, the patient should be treated symptomatically, e.g. with acyclovir or other anti-viral agents (see section 4.4) and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, ATC code: L01XX51.

Mechanism of action

Talimogene laherparepvec is an oncolytic immunotherapy that is derived from HSV-1. Talimogene laherparepvec has been modified to replicate within tumors and to produce the immune stimulatory protein human GM-CSF. Talimogene laherparepvec causes the death of tumor cells and the release of tumor-derived antigens. It is thought that together with GM-CSF, it will promote a systemic anti-tumor immune response and an effector T-cell response. Mice that had complete regression of their primary tumors following treatment were resistant to subsequent tumor re-challenge.

The modifications to talimogene laherparepvec from HSV-1 include deletion of ICP34.5 and ICP47. Whereas anti-viral immune responses defend normal cells following infection by talimogene laherparepvec, tumors have been shown to be susceptible to injury and cell death from ICP34.5-deficient HSV-1 viruses, including talimogene laherparepvec. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, thereby enhancing viral replication in tumor cells.

Clinical efficacy and safety

Study 005/05

The safety and efficacy of Imlygic monotherapy compared with subcutaneously administered GM-CSF were evaluated in a phase 3, multinational, open-label, and randomized clinical study of patients with stage IIIB, IIIC, and IV melanoma that was not considered to be surgically resectable.

Previous systemic treatment for melanoma was allowed but not required. Patients with active brain metastases, bone metastases, extensive visceral disease, primary ocular or mucosal melanoma, evidence of immunosuppression, or receiving treatment with a systemic anti-herpetic agent were excluded from the study.

Patients were randomized in a 2:1 ratio to receive either Imlygic or GM-CSF (N = 436; 295 Imlygic, 141 GM-CSF). Imlygic was administered by intralesional injection at an initial concentration of 10^6 (1 million) PFU/mL on day 1, followed by a concentration of 10^8 (100 million) PFU/mL on day 21 and every 2 weeks thereafter at a dose of up to 4 mL. GM-CSF was administered subcutaneously at 125 µg/m^2 delivered daily for 14 days followed by a 14-day rest period in repeating intervals.

To allow for delayed immune-mediated anti-tumor effects to occur, patients were treated for a minimum of 6 months or until there were no longer any injectable lesions. During this period, treatment was to continue despite an increase in size in existing lesion(s) and/or development of new lesion(s) unless the patient developed intolerable toxicity or the investigator believed that it was in the best interest of the patient to stop treatment or to be given other therapy for melanoma. After 6 months of treatment, patients were to continue treatment until clinically relevant disease progression (i.e. disease progression associated with a decline in performance status and/or alternative therapy was required in the opinion of the investigator). Patients experiencing a response at 12 months of treatment could continue treatment for up to an additional 6 months. The mean (SD) treatment duration for the intent-to-treat (ITT) population was 15.76 weeks (15.79) in the GM-CSF arm and 26.83 weeks (18.39) in the Imlygic arm. The primary endpoint was durable response rate (DRR) [defined as the percent of patients with complete response (CR) or partial response (PR) maintained continuously for a minimum of 6 months] per blinded central review. The secondary endpoints included overall survival (OS), overall response rate (ORR) [PR + CR], time to response, duration of response, and time to treatment failure (time from randomization until the first episode of clinically relevant disease progression where there is no response achieved after the progression event, or until death).

The mean age was 63 (range: 22 to 94) years; 26.5% were over 65 years old and 23.3% were over 74 years old. The majority of patients, 98%, were caucasian. Male patients comprised 57% of study population and 70% of patients were baseline ECOG 0 performance status. Of the enrolled patients, 22% had stage IVM1c disease and 53% of patients had received prior therapy for melanoma such as chemotherapy and cytokine-based immunotherapy in addition to surgery, adjuvant therapy or radiation. Overall, 58% of all patients enrolled into the study were seropositive for wild-type HSV-1 at baseline and 32.6% were seronegative; the HSV-1 serostatus of the remaining 9.4% was unknown.

The difference in DRR between Imlygic and GM-CSF in the ITT population was statistically significant (see table 4) in favor of Imlygic.

Table 4: Summary of results for the ITT population from Imlygic study 005/05

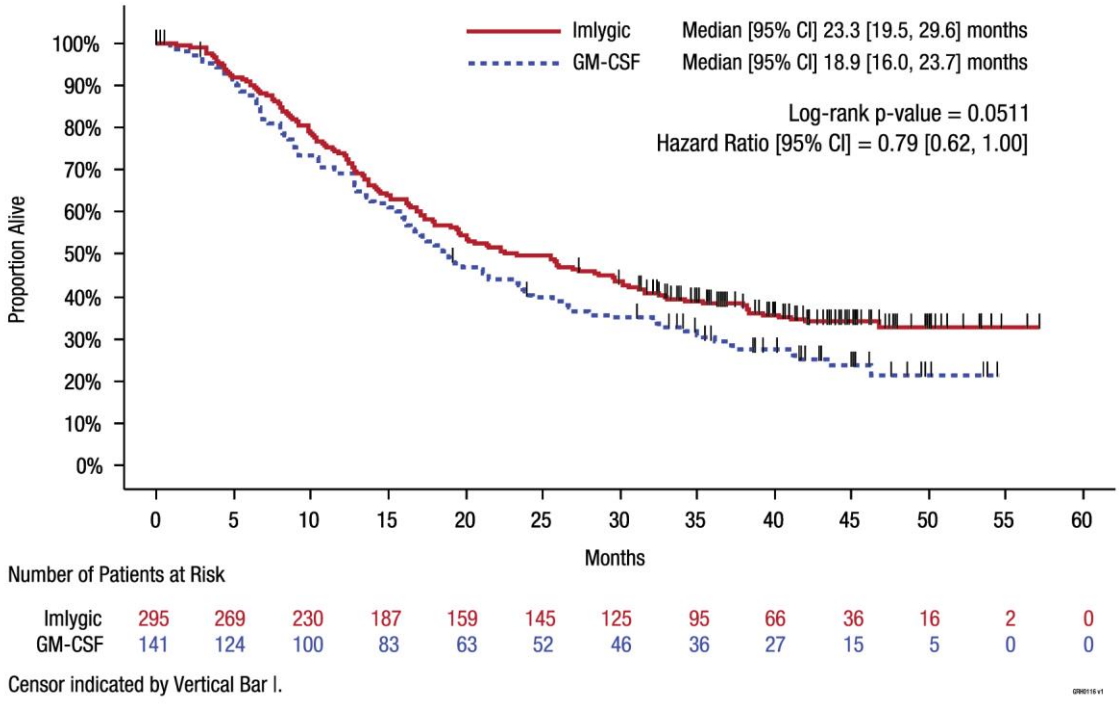
	Study endpoint	**Imlygic N = 295**	**GM-CSF N = 141**
Durable response rate	Primary	16.3% (n = 48) (95% CI: 12.1, 20.5)	2.1% (n = 3) (95% CI: 0.0, 4.5)
		Odds ratio 8.9; (95% CI: 2.7, 29.2) P < 0.0001	
Overall response rate (% CR, % PR)	Secondary	26.4% (n = 78) (95% CI: 21.4%, 31.5%) (10.8% CR, 15.6% PR)	5.7% (n = 8) (95% CI: 1.9%, 9.5%) (0.7% CR, 5% PR)
Overall survival	Secondary	Median 23.3 (95% CI: 19.5, 29.6) months	Median 18.9 (95% CI: 16.0, 23.7) months
		HR: 0.79; (95% CI: 0.62, 1.00) p = 0.051	

	Study endpoint	Imlygic N = 295	GM-CSF N = 141
Duration of response (ongoing response at last tumor evaluation)	Secondary	Not reached (Range: > 0.0 to > 16.8 months)	Median 2.8 months (Range: 1.2 to > 14.9 months)
		HR: 0.46; (95% CI: 0.35, 0.60)	
Time to response (median)	Secondary	4.1 months	3.7 months
Time to treatment failure (median)	Secondary	8.2 months (95% CI: 6.5, 9.9)	2.9 months (95% CI: 2.8, 4.0)
		HR: 0.42; (95% CI: 0.32, 0.54)	

Among the Imlygic-treated responders, 56 (72%) responses were still ongoing at the time of primary analysis. Of the responders, 42 (54%) experienced a ≥ 25% increase in overall size of existing lesion(s) and/or developed a new lesion(s) prior to ultimately achieving a response.

In an analysis to evaluate systemic activity of Imlygic, 27 of 79 patients (34.2%) had a ≥ 50% overall decrease in non-visceral lesions that were not injected with Imlygic, and 8 of 71 patients (11.3%) had a ≥ 50% overall decrease in visceral lesions that were not injected with Imlygic.

Figure 4: Kaplan-Meier plot –overall survival (ITT population)



No overall differences in safety or efficacy were observed between elderly (≥ 65 years old) and younger adult patients.

Exploratory subgroups

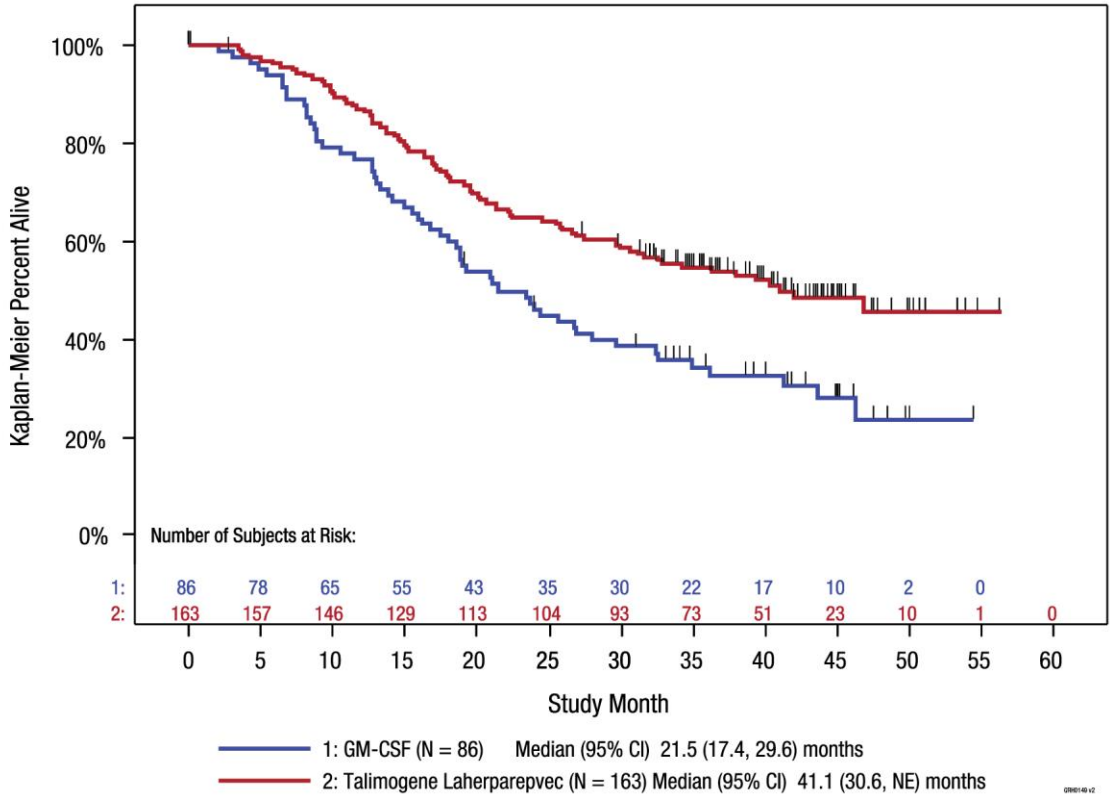
Exploratory subgroup analyses for DRR and overall survival by stage of disease were also carried out (see figure 5 and table 5). While the pivotal study was not powered to evaluate efficacy in these individual subgroups, patients with no visceral disease derived greater benefit from Imlygic treatment than those with more advanced disease.

Table 5: Summary of results from exploratory subgroup analysis from Imlygic study 005/05

	DRR, (%)		ORR, (%)		OS (hazard ratio)
	Imlygic	**GM-CSF**	**Imlygic**	**GM-CSF**	**Imlygic vs GM-CSF**
Stage[§] IIIB/IIIC/ stage IVM1a (Imlygic, n = 163; GM-CSF, n = 86)	25.2	1.2	40.5	2.3	0.57, (95% CI: 0.40, 0.80);
Stage[§] IVM1B/ IVM1C (Imlygic, n = 131; GM-CSF, n = 55)	5.3	3.6	9.2	10.9	1.07, (95% CI: 0.75, 1.52);

[§] American Joint Committee on Cancer (AJCC) staging 6th edition.

Figure 5: Kaplan-Meier estimate of overall survival by randomized treatment arm for disease stage IIIB/IIIC/ stage IVM1a (exploratory subgroup analysis)



Censor indicated by vertical bar |
NE = not estimable

Due to the exploratory nature of the analysis and based on the current evidence, it has not been established that Imlygic is associated with an effect on overall survival.

Pediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Imlygic in one or more subsets of the pediatric population in melanoma (see section 4.2 for information on pediatric use).

5.2 Pharmacokinetic properties

Talimogene laherparepvec is a genetically modified and replication-competent HSV-1 virus. Therefore, its pharmacokinetics and biodistribution are driven by the site of intralesional injection, tumor-selective replication, and release from tumor tissue.

Absorption

Cellular uptake of talimogene laherparepvec occurs through HSV-1 receptors on tumors and non-tumor cells following local injection into tumors. As talimogene laherparepvec is injected and replicates intratumorally, bioavailability and systemic concentration of talimogene laherparepvec are not predictive of drug substance activity and therefore have not been evaluated.

Metabolism/elimination

Talimogene laherparepvec is cleared through general host-defence mechanisms (e.g. autophagy, adaptive immune responses). Talimogene laherparepvec is degraded by typical endogenous protein and DNA catabolic pathways. As with other wild-type HSV-1 infections, a latent pool of talimogene laherparepvec DNA may persist in neuronal cell bodies innervating the injection sites; therefore, the occurrence of latent infection with talimogene laherparepvec cannot be excluded.

Biodistribution (within the body) and viral shedding (excretion/secretion)

Talimogene laherparepvec DNA was quantified with a highly sensitive and specific quantitative Polymerase Chain Reaction (qPCR) assay which may not correlate with viral infectivity risk. Talimogene laherparepvec was also quantified in selected patient samples in clinical studies using viral infectivity assays at the injection sites and in some cases of potential herpetic lesions.

Clinical biodistribution, elimination, and shedding

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 at a dose and schedule same as clinical study 005/05 (see section 5.1). Occlusive dressings samples were collected during treatment. Blood and urine samples were collected during treatment and for up to 30 days after the end of treatment. Injection site, oral mucosa, and anogenital area samples were collected during treatment and for up to 60 days after the end of treatment. Suspected herpetic lesion samples were collected any time a patient experienced lesions of suspected herpetic origin. If the qPCR testing for talimogene laherparepvec DNA was positive, then a $TCID_{50}$ assay was performed to measure viral infectivity. In the 60 patients treated, data indicate that talimogene laherparepvec DNA was present in all sites during the study (see table 6).

Table 6: Patients with detectable DNA during treatment

Body fluid/site	Patients with detectable DNA during treatment (n = 60)
Blood	59 (98%)
Urine	19 (32%)
Injection site	60 (100%)
Exterior of the occlusive dressing	48 (80%)

Body fluid/site	Patients with detectable DNA during treatment (n = 60)
Oral mucosa	8 (13%)
Anogenital area	5 (19%)[a]

[a] For the anogenital area, 26 patients were tested for Imlygic DNA.

The proportion of samples and subjects with talimogene laherparepvec DNA was highest during cycle 2 of treatment for the blood, urine, injection site, and occlusive dressings; highest in cycle 1 of treatment for the oral mucosa; and highest in cycles 1 and 2 for the anogenital area. Among patients with detectable talimogene laherparepvec DNA in the blood, urine, oral mucosa, and anogenital area, no samples had detectable talimogene laherparepvec DNA 30 days after the end of treatment. For patients with detectable DNA in injected lesions, no samples had detectable talimogene laherparepvec DNA 60 days after end of treatment.

Overall 3 of 19 patients with lesions of suspected herpetic origin had talimogene laherparepvec DNA present at any time during the study. Viral activity was measured in samples that were positive for talimogene laherparepvec DNA from the injection site, occlusive dressings, oral mucosa, anogenital area, and suspected herpetic lesions. 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.

Pharmacokinetics in special populations

No pharmacokinetic studies using talimogene laherparepvec have been conducted in special populations.

5.3 Preclinical safety data

At doses up to 4×10^8 PFU/kg or 10^7 PFU/dose (60-fold over the highest proposed clinical dose), single or repeated doses of talimogene laherparepvec administered by SC, IV, or intratumoral injection were well tolerated in immunocompetent mice, rats, and dogs. No neuropathology or adverse neurological effects were observed. In an *in vivo* study of intracerebral injection, talimogene laherparepvec was 10,000-fold less neurovirulent as compared to the wild-type HSV-1 dose that results in death 50% of the time in mice.

Talimogene laherparepvec was injected into various xenograft tumors at doses up to 2×10^8 PFU/kg (30-fold over the highest proposed clinical dose) in immunodeficient mice (nude and SCID). Lethal systemic viral infection was observed in up to 20% of nude mice (primarily deficient in T lymphocyte function) and 100% of SCID mice (devoid of both T and B lymphocytes).

Across studies, fatal disseminated viral infection was observed in 14% of nude mice following treatment with talimogene laherparepvec at doses that are 10 to 100-fold higher than those that result in 100% lethality with wild-type HSV-1.

Mutagenicity

The genotoxic potential of talimogene laherparepvec has not been evaluated in long-term animal or human studies. Because wild-type HSV-1 does not integrate into the host genome, the risk of insertional mutagenesis with talimogene laherparepvec is negligible.

Carcinogenicity

The carcinogenic potential of talimogene laherparepvec has not been evaluated in long-term animal or human studies. However, available data for talimogene laherparepvec and wild-type HSV-1 do not indicate a carcinogenic risk in humans.

Reproductive and development toxicity

There were no impacts to male or female reproductive tissues following treatment of adult mice at doses up to 4×10^8 PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). No effects on embryo-fetal development were observed when talimogene laherparepvec was administered during organogenesis to pregnant mice at doses up to 4×10^8 (400 million) PFU/kg (60-fold higher, on a PFU/kg basis, compared to the maximum clinical dose). Negligible amounts (< 0.001% of maternal blood levels) of talimogene laherparepvec DNA were found in fetal blood.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Di-sodium phosphate dihydrate
Sodium dihydrogen phosphate dihydrate
Sodium chloride
Myo-inositol
Sorbitol (E420)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

After thawing, administer Imlygic as soon as practically feasible.

Thawed Imlygic is stable when stored at temperatures of 2°C up to 25°C protected from light in its original vial, in a syringe, or in the original vial followed by a syringe. Do not exceed the storage times specified in table 7 and table 8.

If storing thawed Imlygic in the original vial followed by a syringe:
- The same temperature range should be maintained throughout the duration of storage until administration.
- The storage time in the syringe at ambient temperature up to 25°C cannot exceed 2 hours for 10^6 (1 million) PFU/mL and 4 hours for 10^8 (100 million) PFU/mL (see table 7).
- The maximum cumulative storage time (storage time in vial plus storage time in syringe) cannot exceed the durations in table 8.

Imlygic must not be refrozen once it has thawed. Discard any thawed Imlygic in the vial or syringe stored longer than the specified times below.

Table 7: Maximum storage time for thawed Imlygic in syringe

	10^6 (1 million) PFU/mL	**10^8 (100 million) PFU/mL**
2°C to 8°C	8 hours	8 hours
up to 25°C	2 hours	4 hours

Table 8: Maximum cumulative storage time (storage time in vial plus storage time in syringe) for thawed Imlygic

	10^6 (1 million) PFU/mL	**10^8 (100 million) PFU/mL**
2°C to 8°C	24 hours	1 week (7 days)
up to 25°C	12 hours	24 hours

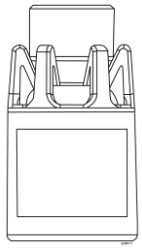
6.4 Special precautions for storage

Store and transport frozen (-90°C to -70°C).
Store in the original carton in order to protect from light.
For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Imlygic is provided as a one mL preservative-free solution in a single–use vial (cyclic olefin polymer plastic resin) with stopper (chlorobutyl elastomer) and seal (aluminum) with flip-off cap (polypropylene) in two different presentations:

Figure 6: Single-use vial permanently inserted into a clear copolyester plastic sleeve



OR

Figure 7: Single-use vial without a clear plastic sleeve

The vial cap is color coded: 10^6 (1 million) PFU/mL is light green and 10^8 (100 million) PFU/mL is royal blue.

6.6 Special precautions for disposal and other handling

Thawing Imlygic vials

- Before use, thaw frozen Imlygic vials at room temperature (20°C to 25°C) until Imlygic is liquid (approximately 30 minutes). Gently swirl. Do NOT shake.
- Vials should be thawed and stored in the original carton until administration in order to protect from light.

Handling and Administration

Follow local guidelines for handling and administration, personal protective equipment, accidental spills, and waste disposal.

- Wear protective gown or laboratory coat, safety glasses, or face shield and gloves while preparing or administering Imlygic. Cover any exposed wounds before administering. Avoid contact with skin, eyes or mucous membranes.
- After administration, change gloves prior to applying occlusive dressings to injected lesions. Wipe the exterior of occlusive dressing with an alcohol wipe. It is recommended to keep injection sites covered with airtight and watertight dressings at all times, if possible. To minimize the risk of viral transmission, patients should keep their injection site covered for at least 8 days from the last treatment or longer if the injection site is weeping or oozing. Advise patients to apply dressing as instructed by the healthcare professional and to replace the dressing if it falls off.
- Dispose of all materials that have come in contact with Imlygic (e.g. vial, syringe, needle, any cotton or gauze) in accordance with local procedures.

Accidental exposure

- In the event of an accidental occupational exposure to Imlygic (e.g. through a splash to the eyes or mucous membranes) during preparation or administration, flush with clean water for at least 15 minutes. In the event of exposure to broken skin or needle stick, clean the affected area thoroughly with soap and water and/or disinfectant.
- Treat all Imlygic spills with a virucidal agent and absorbent materials.
- Advise patients to place used dressings and cleaning materials in a sealed plastic bag as they may be potentially contaminated, and to dispose of the bag in household waste.

This medicine contains genetically modified organisms.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Amgen Europe B.V.
Minervum 7061
NL-4817 ZK Breda
The Netherlands

8. REGISTRATION HOLDER

Amgen Europe B.V.
P.O. BOX 53313
Tel - Aviv
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9. LICENSE NUMBER

160 08 34977
160 09 34978