

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMLYGIC™ safely and effectively. See full prescribing information for IMLYGIC.

IMLYGIC (talimogene laherparepvec)
Suspension for intralesional injection

Initial U.S. Approval: 2015

INDICATIONS AND USAGE

IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Limitation of use: IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases. (1)

DOSAGE AND ADMINISTRATION

- Administer IMLYGIC by injection into cutaneous, subcutaneous, and/or nodal lesions. (2)
- Recommended starting dose is up to a maximum of 4 mL of IMLYGIC at a concentration of 10^6 (1 million) plaque-forming units (PFU) per mL. Subsequent doses should be administered up to 4 mL of IMLYGIC at a concentration of 10^8 (100 million) PFU per mL. (2)

DOSAGE FORMS AND STRENGTHS

Injection: 10^6 (1 million) PFU per mL, 10^8 (100 million) PFU per mL in single-use vials (3)

CONTRAINDICATIONS

- Immunocompromised Patients (4.1)
- Pregnant Patients (4.2)

WARNINGS AND PRECAUTIONS

- Accidental Exposure to IMLYGIC:** Accidental exposure may lead to transmission of IMLYGIC and herpetic infection. Healthcare providers and close contacts should avoid direct contact with injected lesions, dressings, or body fluids of treated patients. Healthcare providers who are immunocompromised or pregnant should not prepare or administer IMLYGIC. If accidental exposure occurs, exposed individuals should clean the affected area. (5.1)

- Herpetic Infection:** Patients who develop herpetic infections should be advised to follow standard hygienic practices to prevent viral transmission. (5.2)
- Injection Site Complications:** Consider the risks and benefits before continuing IMLYGIC treatment if persistent infection or delayed healing develops. (5.3)
- Immune-Mediated Events:** Consider the risks and benefits of IMLYGIC before initiating treatment in patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events. (5.4)
- Plasmacytoma at Injection Site:** Consider the risks and benefits in patients with multiple myeloma or in whom plasmacytoma develops during treatment. (5.5)

ADVERSE REACTIONS

The most commonly reported adverse drug reactions ($\geq 25\%$) in IMLYGIC-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen at 1-855-IMLYGIC (1-855-465-9442) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy:** Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with IMLYGIC. (8.1)
- Lactation:** Discontinue drug or nursing. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dose
- 2.2 Preparation and Handling
- 2.3 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Immunocompromised Patients
- 4.2 Pregnant Patients

5 WARNINGS AND PRECAUTIONS

- 5.1 Accidental Exposure to IMLYGIC
- 5.2 Herpetic Infection
- 5.3 Injection Site Complications
- 5.4 Immune-Mediated Events
- 5.5 Plasmacytoma at Injection Site

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Limitations of use: IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

2 DOSAGE AND ADMINISTRATION

For intralesional injection only. Do not administer intravenously.

2.1 Dose

Administer IMLYGIC by injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance.

IMLYGIC is provided in single-use vials of 1 mL each in two different dose strengths:

- 10^6 (1 million) plaque-forming units (PFU) per mL (light green cap) – for initial dose only
- 10^8 (100 million) PFU per mL (royal blue cap) – for all subsequent doses

Recommended Dose and Schedule

The total injection volume for each treatment visit should not exceed 4 mL for all injected lesions combined. It may not be possible to inject all lesions at each treatment visit or over the full course of treatment. Previously injected and/or uninjected lesion(s) may be injected at subsequent treatment visits. The initial recommended dose is up to 4 mL of IMLYGIC at a concentration of 10^6 (1 million) PFU per mL. The recommended dose for subsequent administrations is up to 4 mL of IMLYGIC at a concentration of 10^8 (100 million) PFU per mL. The recommended dosing schedule for IMLYGIC is shown in Table 1.

Table 1. Recommended Dose and Schedule for IMLYGIC

Treatment	Treatment Interval	Maximum Injection Volume per Treatment Visit (all lesions combined)	Dose Strength	Prioritization of Lesions to be Injected
Initial	–	4 mL	10 ⁶ (1 million) PFU per mL	<ul style="list-style-type: none"> • Inject largest lesion(s) first. • Prioritize injection of remaining lesion(s) based on lesion size until maximum injection volume is reached or until all injectable lesion(s) have been treated.
Second	3 weeks after initial treatment	4 mL	10 ⁸ (100 million) PFU per mL	<ul style="list-style-type: none"> • Inject any new lesion(s) (lesions that have developed since initial treatment) first. • Prioritize injection of remaining lesion(s) based on lesion size until maximum injection volume is reached or until all injectable lesion(s) have been treated.
All subsequent treatments (including reinitiation)	2 weeks after previous treatment	4 mL	10 ⁸ (100 million) PFU per mL	<ul style="list-style-type: none"> • Inject any new lesion(s) (lesions that have developed since previous treatment) first. • Prioritize injection of remaining lesion(s) based on lesion size until maximum injection volume is reached or until all injectable lesion(s) have been treated.

Dose Volume Determination (per Lesion)

Use Table 2 to determine the volume of IMLYGIC injection for each lesion.

Table 2. Determination of IMLYGIC Injection Volume Based on Lesion Size

Lesion Size (longest dimension)	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

When lesions are clustered together, inject them as a single lesion according to Table 2.

Continue IMLYGIC treatment for at least 6 months unless other treatment is required or until there are no injectable lesions to treat.

Reinitiate IMLYGIC treatment if new unresectable cutaneous, subcutaneous, or nodal lesions appear after a complete response.

2.2 Preparation and Handling

Healthcare providers who are immunocompromised or pregnant should not prepare or administer IMLYGIC and should not come into direct contact with the IMLYGIC injection sites, dressings, or body fluids of treated patients [see *Warnings and Precautions (5.1)*].

Avoid accidental exposure to IMLYGIC and follow universal biohazard precautions for preparation, administration, and handling of IMLYGIC:

- Wear personal protective equipment (protective gown or laboratory coat, safety glasses or face shield, and gloves) while preparing or administering IMLYGIC.
- Avoid accidental exposure to IMLYGIC, especially contact with skin, eyes, and mucous membranes.
 - Cover any exposed wounds before handling.
 - In the event of an accidental occupational exposure (e.g., through a splash to the eyes or mucous membranes), 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 a disinfectant.
- Treat all IMLYGIC spills with a virucidal agent such as 1% sodium hypochlorite and blot using absorbent materials.
- Dispose of all materials that may have come in contact with IMLYGIC (e.g., vial, syringe, needle, cotton gauze, gloves, masks, or dressings) in accordance with universal biohazard precautions.
- Advise patients to place used dressings and cleaning materials into a sealed plastic bag and dispose in household waste.

Thawing IMLYGIC Vials

1. Determine the total volume required for injection, up to 4 ml [see *Dosage and Administration (2.1)*].
2. Thaw frozen IMLYGIC vials at room temperature [20° to 25°C (68° to 77°F)] until IMLYGIC is liquid (approximately 30 minutes). Do not expose the vial to higher temperatures. Keep the vial in original carton during thawing.
3. Swirl gently. Do NOT shake.
4. After thawing, administer IMLYGIC immediately or store in its original vial and carton, protected from light in a refrigerator [2° to 8°C (36° to 46°F)] for no longer than the specified duration in Table 3. Do not refreeze IMLYGIC after thawing. Discard any IMLYGIC vial left in the refrigerator longer than the specified times in Table 3.

Table 3. Storage Times for Thawed IMLYGIC Vial at 2° to 8°C (36° to 46°F)

10⁶ (1million)PFUpermL	10⁸ (100million)PFUpermL
12 hours	48 hours

5. Prepare sterile syringes and needles. A detachable needle of 18–26G may be used for IMLYGIC withdrawal and a detachable needle of 22–26G may be used for injection. Small unit syringes (e.g., 0.5 mL insulin syringes) are recommended for better injection control.
6. Using aseptic technique, remove the vial cap and withdraw the product from the vial into the syringe(s), noting the total volume. Avoid generating aerosols when loading syringes with product, and use a biologic safety cabinet if available.

2.3 Administration

Follow the steps below to administer IMLYGIC to patients:

Pre-Injection

1. Clean the lesion and surrounding areas with an alcohol swab and let dry.
2. Treat the injection site with a topical or local anesthetic agent, if necessary. Do not inject anesthetic agent directly into the lesion. Inject anesthetic agent around the periphery of the lesion.

Injection

1. Inject IMLYGIC intralesionally into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance. 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.

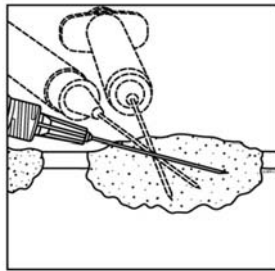


Figure 1: Injection administration for cutaneous lesions

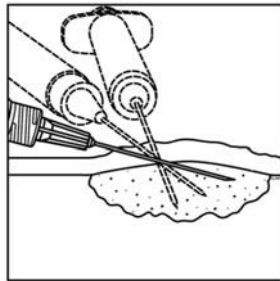


Figure 2: Injection administration for subcutaneous lesions

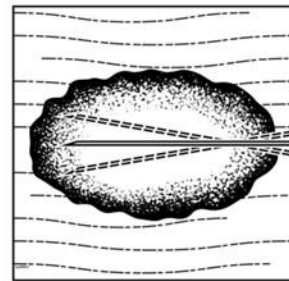


Figure 3: Injection administration for nodal lesions

2. Inject 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 of IMLYGIC. Continue until the full dose is evenly and completely dispersed.
3. When removing the needle, withdraw it from the lesion slowly to avoid leakage of IMLYGIC at the insertion point.
4. Repeat steps 1-2 under pre-injection and steps 1-3 under injection for other lesions to be injected.
5. Use a new needle any time the needle is completely removed from a lesion and each time a different lesion is injected.

Post-Injection

1. Apply pressure to the injection site(s) with sterile gauze for at least 30 seconds.
2. Swab the injection site(s) and surrounding area with alcohol.
3. Change gloves and cover the injected lesion(s) with an absorbent pad and dry occlusive dressing.
4. Wipe the exterior of occlusive dressing with alcohol.
5. Advise patients to:
 - Keep the injection site(s) covered for at least the first week after each treatment visit or longer if the injection site is weeping or oozing.
 - Replace the dressing if it falls off.

3 DOSAGE FORMS AND STRENGTHS

- Initial dose only: 10^6 (1 million) PFU per mL solution in 1 mL single-use vial (light green cap)
- Subsequent doses: 10^8 (100 million) PFU per mL solution in 1 mL single-use vial (royal blue cap)

4 CONTRAINDICATIONS

4.1 Immunocompromised Patients

IMLYGIC is a live, attenuated herpes simplex virus and may cause life-threatening disseminated herpetic infection in patients who are immunocompromised. Do not administer IMLYGIC to immunocompromised patients, including those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy [*see Nonclinical Toxicology (13.2)*].

4.2 Pregnant Patients

Do not administer IMLYGIC to pregnant patients.

5 WARNINGS AND PRECAUTIONS

5.1 Accidental Exposure to IMLYGIC

Accidental exposure may lead to transmission of IMLYGIC and herpetic infection. Accidental needle stick and splashback to the eyes have been reported in healthcare providers during preparation and administration of IMLYGIC.

Healthcare providers, close contacts (household members, caregivers, sex partners, or persons sharing the same bed), pregnant women, and newborns should avoid direct contact with injected lesions, dressings, or body fluids of treated patients [*see Dosage and Administration (2.2)*]. Healthcare providers who are immunocompromised or pregnant should not prepare or administer IMLYGIC.

Caregivers should wear protective gloves when assisting patients in applying or changing occlusive dressings and observe safety precautions for disposal of used dressings, gloves, and cleaning materials [*see Dosage and Administration (2.2)*].

In the event of an accidental exposure to IMLYGIC, exposed individuals should clean the affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, the exposed individuals should contact their healthcare provider for appropriate treatment [*see Warnings and Precautions (5.2)*].

Patients should avoid touching or scratching injection sites or their occlusive dressings, as doing so could lead to inadvertent transfer of IMLYGIC to other areas of the body.

5.2 Herpetic Infection

In clinical studies, herpetic infections (including cold sores and herpetic keratitis) have been reported in patients treated with IMLYGIC. Disseminated herpetic infection may also occur in immunocompromised patients [*see Contraindications (4.1)*].

Patients who develop suspicious herpes-like lesions should follow standard hygienic practices to prevent viral transmission. Patients or close contacts with suspected herpetic infections should also contact their healthcare provider to evaluate the lesions. Suspected herpetic lesions should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442); patients or close contacts have the option of follow-up testing for further characterization of the infection.

IMLYGIC is sensitive to acyclovir. Acyclovir or other antiviral agents may interfere with the effectiveness of IMLYGIC. Therefore, consider the risks and benefits of IMLYGIC treatment before administering antiviral agents to manage herpetic infection.

5.3 Injection Site Complications

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

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). One patient had an amputation of a lower extremity 6 months after IMLYGIC injection due to an infected non-healing wound. This wound area had been treated with surgery and radiation prior to IMLYGIC treatment and had previous wound complications.

If there is persistent infection or delayed healing of the injection site(s), consider the risks and benefits of IMLYGIC before continuing treatment with IMLYGIC.

5.4 Immune-Mediated Events

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

Consider the risks and benefits of IMLYGIC before initiating treatment in patients who have underlying autoimmune disease or before continuing treatment in patients who develop immune-mediated events.

5.5 Plasmacytoma at Injection Site

In a clinical study, a plasmacytoma has been reported in proximity to the injection site after administration of IMLYGIC in a patient with smoldering multiple myeloma.

Consider the risks and benefits of IMLYGIC in patients with multiple myeloma or in whom plasmacytoma develops during treatment.

6 ADVERSE REACTIONS

The most commonly reported adverse drug reactions ($\geq 25\%$) in IMLYGIC-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain.

The following adverse reactions are discussed in greater detail in another section of the label:

- Herpetic Infection [*see Warnings and Precautions (5.2)*]
- Injection Site Complications [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IMLYGIC was evaluated in 419 patients who received at least 1 dose of either IMLYGIC (n = 292) or subcutaneously administered granulocyte-macrophage colony-stimulating factor (GM-CSF) (n = 127) in an open-label, randomized clinical study of patients with stage IIIB, IIIC, and IV melanoma that was not considered to be surgically resectable [*see Clinical Studies (14)*]. The median duration of exposure to IMLYGIC was 23 weeks (5.3 months). Twenty-six patients were exposed to IMLYGIC for at least 1 year.

Most adverse reactions reported were mild or moderate in severity and generally resolved within 72 hours. The most common grade 3 or higher adverse reaction was cellulitis [see *Warnings and Precautions (5.3)*].

Pyrexia, chills, and influenza-like illness can occur any time during IMLYGIC treatment but were more frequent during the first 3 months of treatment.

Table 4 below lists adverse reactions with a 5% or greater incidence in the IMLYGIC arm compared to the GM-CSF arm in the clinical study [see *Clinical Studies (14)*].

Table 4. Adverse Reactions Reported with At Least a 5% Greater Incidence in Patients Treated with IMLYGIC Compared to GM-CSF

Adverse Reactions	IMLYGIC (n = 292)		GM-CSF (n = 127)	
	Any Grade n (%)	Grade 3 n (%)	Any Grade n (%)	Grade 3 n (%)
General disorders and administration site conditions				
Fatigue	147 (50.3)	6 (2.1)	46 (36.2)	1 (< 1)
Chills	142 (48.6)		11 (8.7)	
Pyrexia	125 (42.8)		11 (8.7)	
Influenza-like illness	89 (30.5)	2 (< 1)	19 (15.0)	
Injection site pain	81 (27.7)	2 (< 1)	8 (6.3)	
Gastrointestinal disorders				
Nausea	104 (35.6)	1 (< 1)	25 (19.7)	
Vomiting	62 (21.2)	5 (1.7)	12 (9.5)	
Diarrhea	55 (18.8)	1 (< 1)	14 (11.0)	
Constipation	34 (11.6)		8 (6.3)	1 (< 1)
Abdominal pain	26 (8.9)	2 (< 1)	3 (2.4)	
Musculoskeletal and connective tissue disorders				
Myalgia	51 (17.5)	1 (< 1)	7 (5.5)	
Arthralgia	50 (17.1)	2 (< 1)	11 (8.7)	
Pain in extremity	48 (16.4)	4 (1.4)	12 (9.5)	1 (< 1)
Nervous system disorders				
Headache	55 (18.8)	2 (< 1)	12 (9.5)	
Dizziness	28 (9.6)		4 (3.2)	
Respiratory, thoracic, and mediastinal disorders				
Oropharyngeal pain	17 (5.8)		1 (< 1)	
Investigations				
Weight decreased	17 (5.8)	1 (< 1)	1 (< 1)	

Other adverse reactions associated with IMLYGIC in the open-label, randomized study include glomerulonephritis, vitiligo, cellulitis, and oral herpes.

7 DRUG INTERACTIONS

IMLYGIC is sensitive to acyclovir. Acyclovir or other antiherpetic viral agents may interfere with the effectiveness of IMLYGIC. No drug interaction studies have been conducted with IMLYGIC.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

RiskSummary

Adequate and well-controlled studies with IMLYGIC have not been conducted in pregnant women. No effects on embryo-fetal development have been observed in a study conducted in pregnant mice. The design of the study limits application of the animal data to humans [*see Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

ClinicalConsiderations

If the patient becomes pregnant while taking IMLYGIC, the patient should be apprised of the potential hazards to the fetus and neonate. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with IMLYGIC.

If a pregnant woman has an infection with wild-type Herpes Simplex Virus Type 1 (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 IMLYGIC infections in pregnant women, there could be a risk to the fetus or neonate if IMLYGIC were to act in the same manner.

Data

Animal Data

No effects on embryo-fetal development were observed when IMLYGIC was intravenously administered during organogenesis to immunocompetent pregnant mice at doses up to 4×10^8 (400 million) PFU per kg (60-fold higher, on a PFU per kg basis, compared to the maximum clinical dose). Levels of IMLYGIC DNA in pooled fetal blood were at or below the assay detection level. Study design limitations included: 1) administration of IMLYGIC expressing human granulocyte-macrophage colony-stimulating factor (huGM-CSF), which is not biologically active in mice; 2) unknown transplacental kinetics of IMLYGIC following intravenous administration in pregnant mice; and 3) unknown significance of IMLYGIC dose extrapolation from animal to human based on body weight.

8.2 Lactation

RiskSummary

There is no information regarding the presence of IMLYGIC in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IMLYGIC and any potential adverse effects on the breastfed infant from IMLYGIC or from the underlying maternal condition.

ClinicalConsiderations

Because medicinal products can be found in human milk, a decision should be made whether to discontinue nursing or to discontinue IMLYGIC while nursing.

8.3 Females and Males of Reproductive Potential

No nonclinical or clinical studies were performed to evaluate the effect of IMLYGIC on fertility.

8.4 Pediatric Use

Safety and effectiveness of IMLYGIC have not been established in pediatric patients.

8.5 Geriatric Use

In clinical studies, no overall differences in safety or efficacy were observed between geriatric patients (≥ 65 years old) and younger patients.

8.6 Renal Impairment

No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of IMLYGIC.

8.7 Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of IMLYGIC.

10 OVERDOSAGE

There is no clinical experience with an overdose with IMLYGIC. Doses up to 4 mL at dose strength of 10^8 (100 million) PFU per mL every 2 weeks (maximum cumulative dose of 222.5×10^8 PFU) have been administered in clinical studies, with no evidence of dose-limiting toxicity. The maximum dose of IMLYGIC that can be safely administered has not been determined. In the event of a suspected overdose, the patient should be treated symptomatically and supportive measures instituted as required [*see Warnings and Precautions (5)*].

11 DESCRIPTION

IMLYGIC (talimogene laherparepvec) is a sterile suspension for intralesional injection. IMLYGIC is a live, attenuated HSV-1 that has been genetically modified to express huGM-CSF. The parental virus for IMLYGIC was a primary isolate, which was subsequently altered using recombinant methods to result in gene deletions and insertions.

Each vial contains 1 mL deliverable volume of IMLYGIC at either 1×10^6 (1 million) PFU per mL or 1×10^8 (100 million) PFU per mL concentrations and the following excipients: di-sodium hydrogen phosphate dihydrate (15.4 mg), sodium dihydrogen phosphate dihydrate (2.44 mg), sodium chloride (8.5 mg), myo-inositol (40 mg), sorbitol (20 mg), and water for injection.

The 10^6 (1 million) PFU per mL vial of IMLYGIC contains a clear to semi-translucent liquid following thaw from its frozen state. The 10^8 (100 million) PFU per mL vial of IMLYGIC contains a semi-translucent to opaque liquid following thaw from its frozen state. The liquid in each vial may contain white, visible, variously shaped, virus-containing particles.

Each vial of IMLYGIC may also contain residual components of VERO cells including DNA and protein and trace quantities of fetal bovine serum.

The product contains no preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

IMLYGIC has been genetically modified to replicate within tumors and to produce the immune stimulatory protein GM-CSF. IMLYGIC causes lysis of tumors, followed by release of tumor-derived antigens, which together with virally derived GM-CSF may promote an antitumor immune response. However, the exact mechanism of action is unknown.

12.3 Pharmacokinetics

Biodistribution (within the body) and Viral Shedding (excretion/secretion)

IMLYGIC viral DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay. Infectious IMLYGIC at the injection sites and at some potential herpetic lesions was also quantified using viral infectivity assays.

Nonclinical data

Following repeat intratumoral administration in mice, IMLYGIC DNA was primarily detected in the tumor, blood, spleen, lymph node, liver, heart, and kidney. IMLYGIC DNA was not detected in bone marrow, eyes, lachrymal glands, nasal mucosa, or feces. The highest level of IMLYGIC DNA was found in the injected tumor. IMLYGIC DNA was found in the injected tumor through 84 days and in blood samples through 14 days after the last administration of IMLYGIC.

Clinical data

The biodistribution and shedding of intralesionally administered IMLYGIC are being investigated in an ongoing study measuring IMLYGIC DNA and virus in blood, oral mucosa, urine, injection site, and occlusive dressings. In the initial 20 patients with melanoma who received IMLYGIC intralesional injection at a dose and schedule similar to that of the clinical study [see *Clinical Studies (14)*], available data indicate that IMLYGIC DNA was present in the blood in 17 (85%) patients and in urine of 4 (20%) patients during the study. The peak levels of IMLYGIC DNA in the urine were detected on the day of treatment. Infectious IMLYGIC virus was detected at the site of injection in 3 (15%) patients at a single time point each, and all within the first week after the initial injection. The exterior of the occlusive dressings was positive for IMLYGIC DNA in 14 (70%) patients during the study; however, no infectious virus was detected on the exterior of the occlusive dressing. The number of patients with measurable levels of IMLYGIC DNA on the exterior of occlusive dressings declined over time with no measurable DNA by the third treatment in 13 patients tested.

13 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Repeated intratumoral administration at 2×10^8 (200 million) PFU per kg (30-fold maximum proposed clinical dose, extrapolated based on body weight) did not demonstrate any adverse effects in immunocompetent mice. Severe combined immunodeficient (SCID) mice administered repeat intratumoral injections of IMLYGIC at a dose of 30-fold maximum proposed clinical dose developed systemic viral infection (viral inclusion bodies or necrosis in enteric neurons in the gastrointestinal tract, adrenal gland, skin, pancreatic islet cells, eye, pineal gland, and brain).

14 CLINICAL STUDIES

The safety and efficacy of intralesional injections of IMLYGIC compared with subcutaneously administered GM-CSF was evaluated in a multicenter, open-label, randomized clinical study in patients with stage IIIB, IIIC, and IV melanoma that was considered to be not surgically resectable. IMLYGIC was injected into cutaneous, subcutaneous, or nodal melanoma lesions and was not injected into visceral

lesions. Previous systemic treatment for melanoma was allowed. Patients with active cerebral metastases, bony metastases, extensive visceral disease, primary ocular or mucosal melanoma, evidence of immunosuppression, or receiving treatment with a systemic antiherpetic agent were excluded from the study.

The study included 250 (57%) men and 186 (43%) women. The mean age was 63 (range: 22 to 94) years. Most patients (98%) were white. Seventy percent (70%) of patients had baseline Eastern Cooperative Oncology Group (ECOG) performance status of zero. Seventy percent (70%) of patients had stage IV disease (27% M1a; 21% M1b; and 22% M1c), and 30% had stage III disease. Fifty-three percent (53%) of patients had received prior therapy for melanoma (other than or in addition to surgery, adjuvant therapy, or radiation), and 58% were seropositive for wild-type HSV-1 at baseline.

A total of 436 patients were randomized to receive either IMLYGIC (n = 295) or GM-CSF (n = 141). IMLYGIC was administered by intralesional injection at an initial concentration of 10^6 (1 million) PFU per mL on Day 1, followed by a concentration of 10^8 (100 million) PFU per mL on Day 21 and every 2 weeks thereafter, at a dose of up to 4 mL per visit. GM-CSF was administered subcutaneously in 28-day cycles, i.e., $125 \mu\text{g}/\text{m}^2$ daily for 14 days followed by 14 days without GM-CSF administration.

Patients were to be treated for at least 6 months or until there were no injectable lesions. During this period, treatment could 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), up to 12 months. Patients experiencing a response at 12 months after the start of treatment could continue treatment for up to an additional 6 months, unless there were no remaining injectable lesions or disease progression. All patients were to be followed for survival status for at least 36 months.

The major efficacy outcome 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. Tumor responses were determined according to World Health Organization (WHO) response criteria modified to allow patients who developed new lesions or disease progression of existing lesions to continue the treatment and be evaluated later for tumor response.

The DRR was 16.3% in the IMLYGIC arm and 2.1% in the GM-CSF arm in the overall study population. The unadjusted relative risk was 7.6 (95% CI: 2.4, 24.1), with a p-value < 0.0001. The median time to response was 4.1 (range: 1.2 to 16.7) months in the IMLYGIC arm.

There was no statistically significant difference in overall survival (OS) between the IMLYGIC and the GM-CSF arms. The median OS in the overall study population was 22.9 months in the IMLYGIC arm and 19.0 months in the GM-CSF arm (p = 0.116).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- IMLYGIC is provided as a sterile frozen suspension in a single-use, cyclic olefin polymer (COP) plastic resin vial with a chlorobutyl elastomer stopper, aluminum seal, and polypropylene cap. Each vial contains a retrievable minimal volume of 1 mL.
- The vial cap is color coded:

- 10⁶ (1 million) PFU per mL is light green (NDC 55513-078-01).
- 10⁸ (100 million) PFU per mL is royal blue (NDC 55513-079-01).

Storage and Handling

- Store and transport IMLYGIC at –90°C to –70°C (–130°F to –94°F).
- Protect IMLYGIC from light.
- Store IMLYGIC in the carton until use.
- Thaw IMLYGIC immediately prior to administration [*see Dosage and Administration (2.2)*].
- Do not draw IMLYGIC into a syringe until immediately prior to administration [*see Dosage and Administration (2.2)*].

17 PATIENT COUNSELING INFORMATION

Advise patients and/or close contacts to:

- **Read the FDA-approved patient labeling (Medication Guide).**
- Follow instructions below to prevent viral transmission [*see Warnings and Precautions (5.1)*]:
 - Avoid direct contact with injection sites, dressings, or body fluids of patients.
 - Wear gloves when changing dressing.
 - Avoid touching or scratching injection sites.
 - Keep injection sites covered for at least the first week after each treatment visit or longer if the injection site is weeping or oozing. Replace dressing if it falls off.
 - Dispose of used dressings and cleaning materials in household waste in a sealed plastic bag.
- Female patients of childbearing potential should use an effective method of contraception to prevent pregnancy during treatment with IMLYGIC [*see Contraindications (4.2) and Use in Specific Populations (8.1)*].
- Close contacts who are pregnant or immunocompromised should not change dressings or clean injection sites [*see Warnings and Precautions (5.1)*].
- In case of accidental exposure to IMLYGIC, clean the exposed area with soap and water and/or a disinfectant. Patients or close contacts with suspected herpetic infections should contact their healthcare provider to evaluate the lesions. Suspected herpetic lesions should be reported to Amgen at 1-855-IMLYGIC (1-855-465-9442); patients or close contacts have the option of follow-up testing for further characterization of the infection [*see Warnings and Precautions (5.1) and (5.2)*].



IMLYGIC™ (talimogene laherparepvec)

Manufactured by:

BioVex, Inc., a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: <http://pat.amgen.com/Imlygic/>

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