NAME OF THE MEDICINE

IMLYGIC™ is the Amgen Inc. trademark for talimogene laherparepvec (rmv)

DESCRIPTION

Talimogene laherparepvec is 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 **Mechanism of Action**]. Talimogene laherparepvec is produced in vero cells by recombinant DNA technology.

IMLYGIC is a sterile, preservative free solution for intralesional injection. Following thaw the liquid is clear to semi-translucent (10^6 Plaque forming units (PFU)/mL) or semi-translucent to opaque (10^8 PFU/mL) and may contain white, visible, variously shaped, virus-containing particles.

Each single-use vial contains 1 mL deliverable volume of IMLYGIC at a nominal concentration of 1 x 10^6 (1 million) PFU/mL or 1 x 10^8 (100 million) PFU/mL IMLYGIC, and 15.4 mg sodium phosphate - dibasic dihydrate, 2.44 mg sodium phosphate - monobasic dihydrate, 8.5 mg sodium chloride, 40.0 mg inositol, 20 mg sorbitol, in water for injections.

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

IMLYGIC is an oncolytic immunotherapy that is derived from HSV-1. IMLYGIC has been modified to replicate within tumours and to produce the immune stimulatory protein GM-CSF. IMLYGIC causes lytic tumour cell death and release of tumour-derived antigens and GM-CSF, which together promote a systemic anti-tumour immune response.

The modifications to derive IMLYGIC from HSV-1 include deletion of ICP34.5 and ICP47. Whereas anti-viral immune responses defend normal tissues following infection by IMLYGIC, tumours have been shown to be susceptible to injury and cell death from ICP34.5-deficient HSV-1 viruses, including IMLYGIC. GM-CSF recruits and activates antigen presenting cells which can process and present tumour-derived antigens to promote an effector T-cell response.

Pharmacokinetics

IMLYGIC is a genetically modified and replication-competent HSV-1 virus. Therefore, its pharmacokinetics and biodistribution are driven by the site of intralesional injection, tumour-selective replication, and release from tumour tissue. None of the genetic modifications in IMLYGIC are expected to affect the absorption, metabolism, and elimination of IMLYGIC compared to wild-type HSV-1. The biodistribution of IMLYGIC is consistent with tumour-selective replication.

Absorption

Cellular uptake of IMLYGIC occurs through HSV-1 receptors on tumours and non-tumour cells following intralesional injection. As IMLYGIC is injected and replicates intratumourally, neither bioavailability nor systemic concentration of IMLYGIC is predictive of drug activity.

Metabolism/Excretion

IMLYGIC is cleared through general host-defence mechanisms (e.g., autophagy, adaptive immune responses). IMLYGIC is degraded by typical endogenous protein and DNA catabolic pathways. As with other wild-type HSV-1 infections, a latent pool of IMLYGIC DNA may persist in neuronal cell bodies innervating the injection sites. The occurrence of latent infection with IMLYGIC has not been established in humans. However, in a mouse model, latency of IMLYGIC was observed and reactivation could be induced *ex vivo*.

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

IMLYGIC (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. IMLYGIC 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.

Nonclinical Biodistribution, Elimination, and Shedding

Following intralesional administration in mice, IMLYGIC DNA was detected in ~40 % of tumour samples and in ≤ 20% of blood and organ tissue samples (e.g. spleen, lymph node, liver, heart, and kidneys) in the 84 days following injection. IMLYGIC DNA was detected in ≤2% of samples of brain, ovary, and salivary gland, and was not detected in bone marrow, eyes, shedding tissues (lacrimal glands, nasal mucosa), or faeces. The

concentrations of IMLYGIC DNA was generally highest in tumours and other tissues had lower levels of IMLYGIC DNA. IMLYGIC DNA could be found in injected tumours through 84 days after the last dose, but was cleared from the majority (94%) of blood samples by 7 days after the last dose. Following intravenous administration in mice, IMLYGIC DNA was quantifiable in ~17% of peripheral nerve (trigeminal ganglion) samples.

Clinical Biodistribution, Elimination, and Shedding

The biodistribution and shedding of intralesionally administered IMLYGIC are being investigated in a dedicated study. In results from 30 patients included in the interim analysis, IMLYGIC DNA was detected at transient and low concentrations in blood in 90% of individuals and in urine in 20% of individuals in the study. The proportion of individuals with detectable IMLYGIC DNA in blood and urine was highest during the second cycle of treatment. While approximately 90% of individuals had IMLYGIC DNA in samples obtained from the surface of injected lesions, only 14% of individuals tested positive for infective virus by $TCID_{50}$ assay. Seventeen percent of samples from the exterior of occlusive dressing tested positive for IMLYGIC DNA but none tested positive for presence of infective virus. Among the 30 individuals tested for presence for IMLYGIC DNA in oro-labial region, one individual had detectable IMLYGIC DNA, but the sample did not test positive for presence of infective virus.

Special Populations

Elderly

The pharmacokinetic profile has not been assessed in the elderly.

Paediatric

The pharmacokinetic profile has not been assessed in those ≤ 18 years.

Impaired renal function

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

Impaired hepatic function

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

CLINICAL TRIALS

Metastatic Melanoma

Study 1

The safety and efficacy of IMLYGIC compared with subcutaneously administered GM-CSF was evaluated in a phase 3, multicentre, open-label and randomised clinical study of patients with Stage IIIB, IIIC, and IV melanoma that was not considered to be surgically resectable. Patients could have no more than 3 visceral metastases (not including lung metastases or nodal metastases associated with visceral organs), no visceral metastasis could be larger than 3 cm in diameter, and liver lesions had to be stable for at least 1 month. Lactate Dehydrogenase (LDH) could not be more than 1.5 x the upper limit of normal (ULN). In the IMLYGIC arm, 5 % of patients had LDH levels > ULN. Patients with bone metastases or clinically active cerebral metastases, evidence of immunosuppression, patients receiving treatment with a systemic anti-herpetic agent and patients with primary ocular or mucosal melanoma were also excluded.

A total of 436 patients were randomised in a 2:1 ratio 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/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.

The mean age was 63 (range: 22 to 94) years. Male patients comprised of 57% of study population and 70% of patients were baseline ECOG 0 performance status. Of the enrolled patients, 30% had Stage III; 27% had Stage IVM1a; 21% had Stage IVM1b and 22% had Stage IVM1c disease; 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.

To allow for delayed immune-mediated anti-tumour effects to occur, patients were treated for a minimum of 6 months or until no injectable lesions were remaining. During this period, treatment was to continue despite an increase in size of existing lesion(s) and/or development of new lesion(s) unless the patient's clinical condition required initiation of a new therapy. Patients experiencing a response at 12 months of treatment could continue treatment for up to an additional 6 months.

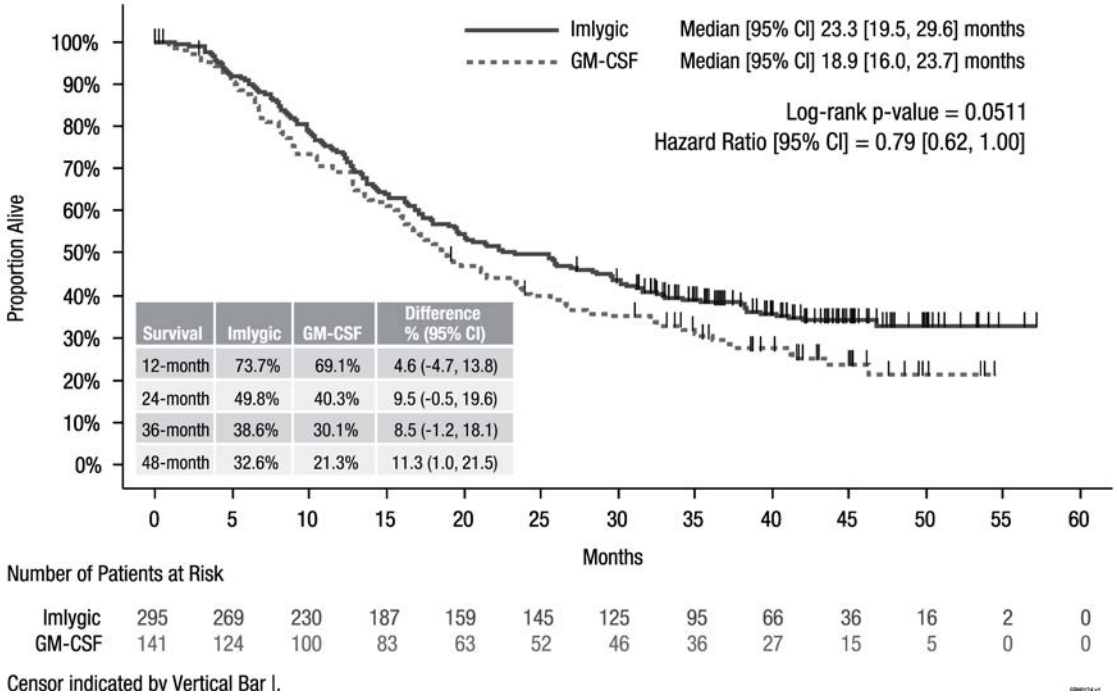
The primary endpoint was durable response rate (DRR) [defined as the percent of patients with complete response (CR) or partial response (PR) maintained continuously for a minimum of 6 months] per blinded central review using modified WHO criteria. The secondary endpoints included overall survival (OS), overall response rate (ORR) [PR+CR], time to response and duration of response. Treatment with IMLYGIC statistically significantly increased DRR in the overall population (Table 1).

There were 78 responders in the IMLYGIC arm and 8 in the GM-CSF arm. Among the IMLYGIC-treated responders, 56 (72%) responses were still ongoing at the time of primary analysis. There was a 65% probability that responses lasted at least 12 months. Of the IMLYGIC responders, 42 (54%) experienced a ≥ 50% increase in overall size of existing lesion(s) and/or developed 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. After treatment with IMLYGIC, 13 IMLYGIC-treated patients underwent surgery with curative intent. Of these, 9 had no evidence of disease after surgery and 4 had a pathologic CR.

In the overall trial population, the median follow up time was 44.4 months and the median OS (95% CI) was 23.3 (19.5, 29.6) months and 18.9 (16.0, 23.7) months for IMLYGIC and GM-CSF, respectively (HR=0.79; 95% CI: 0.62, 1.00; p =0.051) (Figure 1). Among the IMLYGIC-treated patients that achieved a durable response, there was a 96% probability of survival at 3 years.

Figure 1. Kaplan-Meier Plot – OS (Intent to Treat Population)



Censor indicated by Vertical Bar I.

Patients that have not been recorded as deceased are included as censored.

The results for key study endpoints in the intent to treat population are summarised in Table 1.

Table 1. Summary of Results (Intent to Treat Population)

Study Endpoint	Endpoint	IMLYGIC (N=295)	GM-CSF (N=141)
Durable Response Rate (95% CI)	Primary	16.3% (12.1, 20.5)	2.1% (0.0, 4.5)
		Odds ratio 8.9; (95% CI: 2.7, 29.2); p<0.0001	
Overall Response Rate (95% CI) (% CR, % PR)	Secondary	26.4% (21.4, 31.5) (10.8% CR, 15.6% PR)	5.7% (1.9, 9.5) (0.7% CR, 5% PR)
Overall Survival (95% CI)	Secondary	median 23.3 (19.5, 29.6) months	median 18.9 (16.0, 23.7) months
		HR: 0.79; (95% CI: 0.62, 1.00); p = 0.051	
Duration of Response	Secondary	Not reached (Range; >0.0[a] to > 16.8[a] months)	median 2.8 (Range; 1.2 to > 14.9[a] months)

		HR: 0.46; (95% CI: 0.35, 0.60)	
Time to Response (95% CI)	Secondary	median 4.1 months (3.8, 5.4) (Range; 1.2 – 16.7 months)	median 3.7 months (1.9, 5.6) (Range; 1.9 - 9.1 months)
Time to Treatment Failure (95% CI)	Secondary	median 8.2 months (6.5, 9.9)	median 2.9 months (2.8, 4.0)
		HR: 0.42: (95% CI 0.32, 0.54)	

[a] Response ongoing at last evaluation

Exploratory subgroup analyses for DRR, ORR and overall survival by stage of disease were also conducted (Table 2). The pivotal study was not powered to evaluate efficacy in these individual subgroups.

Table 2. Summary of Results from Exploratory Analysis from IMLYGIC Study 1

	DRR (%)		ORR (%)		OS (hazard Ratio)
	IMLYGIC	GM-CSF	IMLYGIC	GM-CSF	IMLYGIC vs GM-CSF
Stage IIIB/IIIC/IVM1a (IMLYGIC, n = 163; GM-CSF, n = 86)	25.2	1.2	40.5	2.3	0.57, (95% CI 0.40, 0.80); p* = 0.0009
Stage IVM1b/M1c (IMLYGIC, n = 131; GM-CSF, n = 55)	5.3	3.6	9.2	10.9	1.07, (95% CI: 0.75, 1.52); p* = 0.7094

*p-values are descriptive

Supportive Data in Melanoma

Study 2

In the single arm open-label phase 2 study investigating IMLYGIC, patients with Stage IIIC or Stage IV melanoma, were treated with up to 24 doses of IMLYGIC. Of the 50 patients enrolled, 14 (28%) achieved a response - 8 (16%) of which were CRs. Three patients received additional treatment with IMLYGIC in an optional extension study, in which one additional CR was observed resulting in a combined overall response rate of 30%. Of the 15 responses that occurred, eight were still ongoing at end of year 1 and two were ongoing at the end of year 2. The safety profile for patients in Study 2 was comparable to that in Study 1.

INDICATIONS

IMLYGIC is indicated as monotherapy for the treatment of melanoma in patients with unresectable cutaneous, subcutaneous or nodal lesions after initial surgery.

CONTRAINDICATIONS

IMLYGIC is contraindicated in patients:

- with known hypersensitivity to talimogene laherparepvec or excipients [see **DESCRIPTION**]
- who are severely immunocompromised (e.g., patients with severe congenital or acquired cellular and/or humoral immune deficiency). These patients may be at risk for life-threatening disseminated herpetic infection [see **PRECAUTIONS**: **Immunocompromised Patients**]

PRECAUTIONS

Immunocompromised Patients

IMLYGIC has not been studied in immunocompromised patients. IMLYGIC was injected into xenograft tumours at doses up to 2 x 10^8 PFU/kg (30-fold over the maximum clinical dose) in immunodeficient mice [nude and with Severe Combined Immunodeficiency (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).

Based on the 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 **CONTRAINDICATIONS**]. Disseminated herpetic infection may also occur in immunocompromised patients (such as those with HIV/AIDS, leukaemia, lymphoma, common variable immunodeficiency, or who require chronic high-dose steroids or other immunosuppressive agents). Consider the risks and benefits of treatment before administering IMLYGIC to these patients.

Accidental Exposure to IMLYGIC

Accidental exposure may lead to transmission of IMLYGIC and herpetic infection. Healthcare providers and close contacts (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 **PHARMACOLOGY** *Clinical Biodistribution and Shedding*]. Healthcare providers who are immunocompromised should not administer IMLYGIC and should not come into direct contact with the IMLYGIC injection sites or body fluids of treated patients [see *Dosage and Administration*]. Accidental needle stick and splash back have been reported in healthcare providers during preparation and administration of IMLYGIC.

Patients should be advised to avoid touching or scratching injection sites as this could lead to inadvertent transfer of IMLYGIC to other areas of their body.

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 with IMLYGIC [see **Use in Pregnancy**].

Close contacts who are pregnant or immunocompromised should not change the patient's dressings or clean their injection sites. Pregnant women, infants less than 3 months old, and immunocompromised individuals should not be exposed to potentially contaminated materials.

Caregivers should be advised to wear protective gloves and cover any exposed wounds when assisting patients in applying or changing occlusive dressings and to observe safety precautions for disposal of used dressings and cleaning materials [see **DOSAGE and ADMINISTRATION Special Instructions for Use and Handling**].

In the event of an accidental exposure to IMLYGIC, exposed individuals should be advised to clean affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, they should contact their healthcare provider.

Neonatal Exposure

Infections with wild-type HSV-1 in a foetus or neonate have been associated with serious adverse effects, including multi-organ failure and death [see **Use in Pregnancy**]. While it is not known if IMLYGIC will behave like HSV-1, neonates should not be exposed to bodily fluids of the treated patient, injection site or contaminated materials. Neonatal herpetic infections have not been reported with IMLYGIC. If infection were to occur, contact a healthcare provider immediately.

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.

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 (1800 803 638); patients or close contacts have the option of follow-up testing for further characterisation of the infection.

IMLYGIC is sensitive to aciclovir. Consider the risks and benefits of IMLYGIC treatment before administering aciclovir or other anti-viral agents indicated for management of herpetic infection. These agents may interfere with the effectiveness of IMLYGIC.

Cellulitis at the Injection Site

Necrosis or ulceration of tumour 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).

Consider the risks and benefits of IMLYGIC before continuing treatment if persistent infection or delayed healing develops.

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.

Plasmacytoma at the Injection Site

Plasmacytoma has been reported in proximity to the injection site after administration of IMLYGIC. Consider the risks and benefits of IMLYGIC in patients with multiple myeloma or in whom plasmacytoma develops during treatment.

Obstructive Airway Disorder

Obstructive airway disorder has been reported following IMLYGIC treatment. Use caution 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 during the first 3 months of treatment [see **ADVERSE EFFECTS**]

Effects on Fertility

No nonclinical or clinical studies have been performed to evaluate the effects of IMLYGIC on fertility. There were no impacts to male or female reproductive tissues following treatment of adult 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).

Use in Pregnancy

Pregnancy Category: C

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 in mice.

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

Transplacental metastases of malignant melanoma can occur. Because IMLYGIC is modified to enter and replicate in the tumour tissue, there could be a risk of fetal

exposure to IMLYGIC from tumour tissue that has crossed the placenta. No effects on embryo-fetal development were observed when IMLYGIC was administered during organogenesis to pregnant mice at doses up to 4 x 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 IMLYGIC DNA were found in fetal blood.

Use in Lactation

It is not known whether IMLYGIC is transferred into human milk. The risk of possible transmission of IMLYGIC through lactation should be considered and patients should be advised to discontinue breastfeeding or to discontinue IMLYGIC prior to breastfeeding.

Paediatric Use

The safety and efficacy of IMLYGIC have not been established in paediatric patients.

Use in the Elderly

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

Carcinogenicity

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

Genotoxicity

The genotoxic potential of IMLYGIC has not been evaluated. Because wild-type HSV-1 does not integrate into the host genome, the risk of insertional mutagenesis with IMLYGIC is negligible.

Effect on Laboratory Tests

Interactions with laboratory tests have not been established.

INTERACTIONS WITH OTHER MEDICINES

No drug interactions studies have been conducted with IMLYGIC.

ADVERSE EFFECTS

The safety of IMLYGIC was evaluated in 419 patients (292 IMLYGIC, 127 GM-CSF) in Study 1 that received at least 1 dose of study treatment. The median duration of exposure to IMLYGIC was 23 weeks (5.3 months). Twenty-six patients were exposed to IMLYGIC for at least one year.

The most commonly reported adverse reactions (≥ 25%) in IMLYGIC-treated patients were fatigue, chills, pyrexia, nausea, influenza like illness, and injection site pain. Ninety-eight percent of these adverse reactions reported were mild or moderate in severity. The most common grade 3 or higher adverse reaction was cellulitis [see **PRECAUTIONS**]. Safety data obtained from 50 patients in Study 2 and extension studies were consistent with data from Study 1. Adverse reactions observed in IMLYGIC clinical trials are listed below by frequency and MedDRA body system organ class.

Very Common (≥ 1 in 10)

General disorders and administration site conditions	Influenza-like illness, Pyrexia, Chills, Fatigue, Pain, Injection site reactions*
Gastrointestinal disorders	Vomiting, Diarrhoea, Constipation, Nausea
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity
Nervous system disorders	Headache
Blood and lymphatic disorders	Oedema peripheral
Respiratory, thoracic and mediastinal disorders	Cough

Common (≥ 1 in 100 to < 1 in 10)

General disorders and administration site conditions	Malaise, Axillary pain
Ear and labyrinth disorders	Ear Pain
Cardiac disorders	Tachycardia
Gastrointestinal disorders	Abdominal Pain, Abdominal discomfort
Musculoskeletal and connective tissue disorders	Back pain, Groin pain
Skin and subcutaneous tissue disorders	Vitiligo, Rash, Dermatitis
Infections and infestations	Cellulitis, Oral Herpes
Nervous System Disorders	Confusional state, Anxiety, Depression, Dizziness, Insomnia
Respiratory, thoracic and mediastinal disorders	Dyspnoea exertional, Oropharyngeal pain, Upper respiratory tract infection
Metabolism and nutrition disorders	Dehydration
Injury, poisoning and procedural complications	Wound complication, Wound secretion, Contusion, Procedural pain
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumour pain, Infected neoplasm
Investigations	Weight decreased
Vascular Disorders	Deep vein thrombosis, Hypertension, Flushing
Blood and lymphatic system disorders	Anaemia

Common (≥ 1 in 100 to < 1 in 10)

Eye disorders	Keratitis herpetic
Infections and infestations	Cellulitis at injection site, Incision site infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Plasmacytoma at injection site
Vascular disorders	Vasculitis
Respiratory, thoracic and mediastinal disorders	Obstructive airways disorder, Pneumonitis
Skin and subcutaneous tissue disorders	Psoriasis

Renal and urinary disorders	Glomerulonephritis

* Injection site reactions include: very common term of injection site pain, common terms of injection site erythema, injection site haemorrhage, injection site swelling, injection site reaction, injection site inflammation, secretion discharge, injection site discharge, uncommon term of injection site warmth.

Table 3 lists adverse events reported in Study 1.

Table 3. Adverse Events Reported in ≥ 10% Incidence in Patients Administered with IMLYGIC or GM-CSF in Study 1 by maximum grade

	IMLYGIC (N = 292)		GM-CSF (N = 127)	
Preferred Term	n (%)	Grade 3 and 4^ n (%)	n (%)	Grade 3 and 4^ n (%)
Fatigue	147 (50.3)	5 (1.7)	46 (36.2)	1 (0.8)
Chills	142 (48.6)	0 (0)	11 (8.7)	0 (0)
Pyrexia	125 (42.8)	0 (0)	11 (8.7)	0 (0)
Nausea	104 (35.6)	1 (0.3)	25 (19.7)	0 (0)
Influenza-like illness	89 (30.5)	2 (0.7)	19 (15.0)	0 (0)
Injection site pain	81 (27.7)	3 (1.0)	8 (6.3)	0 (0)
Vomiting	62 (21.2)	5 (1.7)	12 (9.4)	0 (0)
Diarrhoea	55 (18.8)	1 (0.3)	14 (11.0)	0 (0)
Headache	55 (18.8)	2 (0.7)	12 (9.4)	0 (0)
Myalgia	51 (17.5)	1 (0.3)	7 (5.5)	0 (0)
Arthralgia	50 (17.1)	2 (0.7)	11 (8.7)	0 (0)
Pain in extremity	48 (16.4)	4 (1.4)	12 (9.4)	1 (0.8)
Pain	47 (16.1)	2 (0.7)	13 (10.2)	1 (0.8)
Oedema peripheral	35 (12.0)	2 (0.7)	12 (9.4)	2 (1.6)
Constipation	34 (11.6)	0 (0.0)	8 (6.3)	1 (0.8)
Cough	31 (10.6)	0 (0)	10 (7.9)	0 (0)
Decreased appetite	30 (10.3)	0 (0)	14 (11.0)	0 (0)
Pruritus	28 (9.6)	0 (0)	19 (15.0)	0 (0)
Injection site erythema	15 (5.1)	0 (0)	33 (26.0)	0 (0)
Dyspnoea	13 (4.5)	3 (1.0)	13 (10.2)	3 (2.4)
Injection site pruritus	5 (1.7)	0 (0)	21 (16.5)	0 (0)

^ There were no grade 5 adverse events reports with the exception of Dyspnoea with n=1 (0.8%) Grade 5 event in the GM-CSF arm

Description of selected Adverse Reactions

Influenza-like symptoms

Pyrexia, chills, and influenza like illness, which can occur any time during IMLYGIC treatment, generally resolved within 72 hours. These events were reported more frequently during the first 3 cycles of treatment, particularly in patients who were HSV-1 negative at baseline.

DOSAGE AND ADMINISTRATION

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

Recommended Dose and Schedule

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 same lesion(s) may be injected in more than one treatment visit. The recommended dosing schedule for IMLYGIC is shown in Table 4.

Table 4. Recommended Dosing Schedule for IMLYGIC

Treatment	Treatment interval	Maximum 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 • Prioritise injection of remaining lesion(s) 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	• Inject any new lesion(s) (lesions that may have developed since initial treatment) first • Prioritise injection of remaining lesion(s) based on lesion size until maximum injection volume is reached.
All subsequent treatments (including re-initiation)	2 weeks after previous treatment	Up to 4 mL	10^8 (100 million) PFU/mL	• Inject any new lesion(s) (lesions that may have developed since previous treatment) first • Prioritise injection of remaining lesions based on lesion size until maximum injection volume is reached

Determining IMLYGIC Dose Volume per Lesion

The volume of IMLYGIC to be injected into each lesion is dependent on the size of the lesion and should be determined according to Table 5. The total injection volume for each treatment visit should be up to a maximum of 4 mL.

Table 5. 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

Since patients may experience increase in size of existing lesions or the appearance of new lesion(s) prior to achieving a response, IMLYGIC treatment should be continued where there is opportunity for clinical benefit unless other treatment is required or until no injectable lesions are remaining.

IMLYGIC treatment may be reinitiated if new lesion(s) appear following a complete response.

Method of Administration

Healthcare providers should avoid accidental exposure to IMLYGIC and follow handling instructions while administering the medicine [see **Special Instructions for Use and Handling**].

Healthcare providers who are immunocompromised should not administer IMLYGIC and should not come into direct contact with the IMLYGIC injection sites or body fluids of treated patients [see **CONTRAINDICATIONS** and **PRECAUTIONS Immunocompromised Patients** and **Accidental Exposure to IMLYGIC**].

Follow the instructions below to prepare and administer IMLYGIC to patients

Pre injection

- Thaw IMLYGIC vials at room temperature [see **PRESENTATION AND STORAGE CONDITIONS**].
- Draw desired amount of IMLYGIC from the vial into a syringe. A 22- to 24-gauge needle is recommended.
- The injection site may be treated with a topical anaesthetic agent. Injectable anaesthetic 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 5 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.

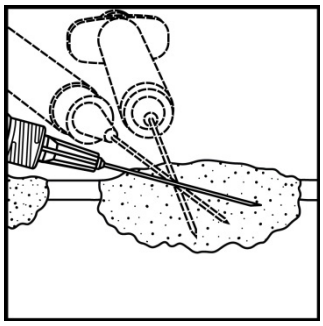


Figure 4. Injection administration for cutaneous lesions

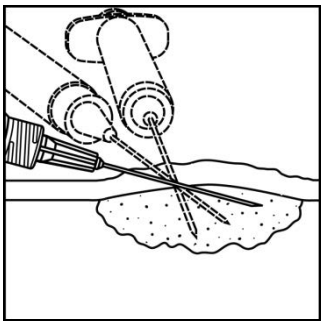


Figure 3. Injection administration for subcutaneous lesion

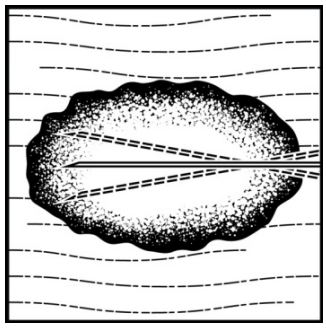


Figure 2. Injection administration for nodal

- 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 of IMLYGIC. 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 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.

Disposal

Dispose of all materials that have come in contact with IMLYGIC (e.g., vial, syringe, needle, any cotton or gauze) in accordance with local institutional procedures [see **Special Instructions for Use and Handling**].

Special Instructions for Use and Handling

Follow local institutional guidelines for handling, 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 and advise patients to keep the injection sites covered at all times and replace 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 institutional procedures.
- 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 and dispose in household waste.

OVERDOSAGE

There is no clinical experience with overdosage 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 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

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

- IMLYGIC must be transported and stored at -90°C to -70°C.
- IMLYGIC should be protected from light.
- IMLYGIC should be stored in the carton until use.
- IMLYGIC should be thawed immediately prior to administration. See thawing instructions below.

IMLYGIC does not contain any antimicrobial preservative or bacteriostatic agent. To reduce microbiological hazard, IMLYGIC should not be drawn into a syringe until immediately prior to administration.

Thawing IMLYGIC vials

- IMLYGIC should only be exposed to room temperature (20ºC to 25ºC) during thawing and administration.
- Before use, thaw frozen IMLYGIC vials at room temperature (20ºC to 25ºC) until IMLYGIC is liquid (approximately 30 minutes). Gently swirl. **DO NOT SHAKE**.
- IMLYGIC must not be refrozen once it has thawed.

- After thawing, IMLYGIC should be administered immediately or should be stored in its original vial, protected from light, in a refrigerator (2°C to 8°C) until administration within the following criteria:

IMLYGIC 10^6 PFU/mL	Up to 12 hours at 2°C to 8°C. Discard any IMLYGIC vial left in a refrigerator longer than this specified time
IMLYGIC 10^8 PFU/mL	Up to 48 hours at 2°C to 8°C. Discard any IMLYGIC vial left in a refrigerator longer than this specified time

NAME AND ADDRESS OF THE SPONSOR

Amgen Australia Pty Ltd
ABN 31 051 057 428
Level 7 123 Epping Road
North Ryde, NSW, 2113.

Medical Information 1800 803 638

POISON SCHEDULE OF THE MEDICINE

S4 Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

21 December 2015