IMLYGIC®
(talimogene laherparepvec)

Physician Education Booklet

INFORMATION FOR PHYSICIANS

RISKS OF TRANSMISSION AND HERPETIC COMPLICATIONS (SAFE USE AND HANDLING OF IMLYGIC®)

THIS PHYSICIAN EDUCATION BROCHURE IS TO INFORM YOU OF:

accidental exposure of healthcare professionals and close contacts to IMLYGIC®	**the risk of herpetic infection including disseminated herpetic infections in treated patients**
information on safe use and handling of IMLYGIC®	**IMLYGIC® use in pregnancy**
the important accompanying patient educational materials	

This brochure does not contain a comprehensive description of the risks associated with IMLYGIC®. Please read the current Summary of Product Characteristics (SmPC) for IMLYGIC® provided with this brochure and available online at https://www.medicines.ie/ or at https://www.hpra.ie/.

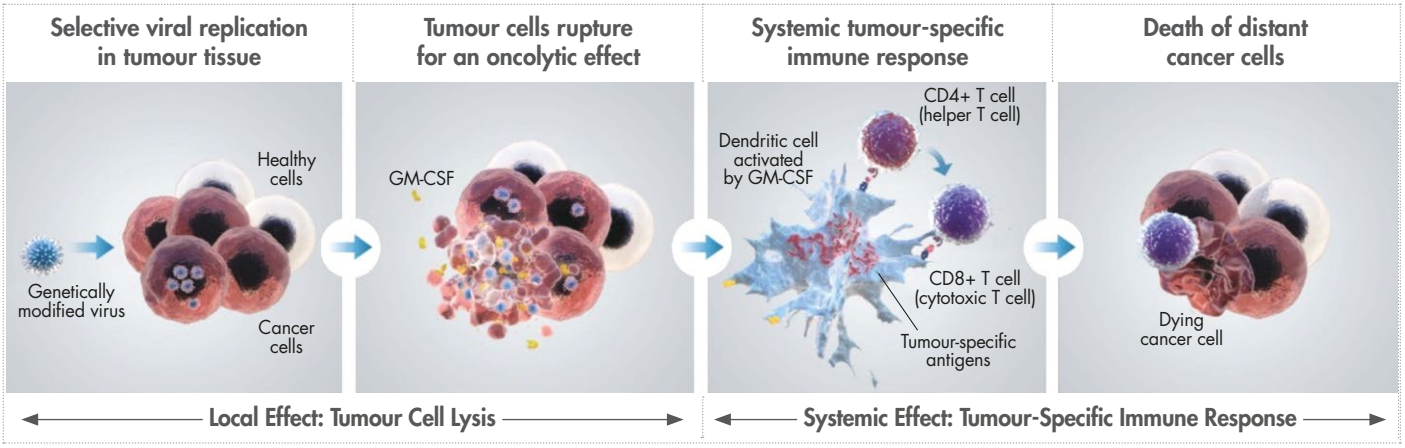
IMLYGIC® is an attenuated herpes simplex virus type 1 (HSV-1) derived by functional deletion of 2 genes (ICP34.5 and ICP47) and insertion of coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF). IMLYGIC® is produced in Vero cells by recombinant DNA technology.

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 SmPC sections 4.4 and 5.1).

IMLYGIC® MECHANISM OF ACTION

IMLYGIC® is an oncolytic immunotherapy that is derived from HSV-1. IMLYGIC® has been modified to efficiently replicate within tumours and to produce the immune stimulatory protein human 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 IMLYGIC® from HSV-1 include deletion of ICP34.5 and ICP47. Deletion of ICP34.5 allows IMLYGIC® replication in tumour tissue; normal cells are able to protect against IMLYGIC® infection as they contain intact anti-viral defense mechanisms. Deletion of ICP47 prevents down-regulation of antigen presentation molecules and increases the expression of HSV US11 gene, which enhances viral replication in tumour cells. GM-CSF recruits and activates antigen presenting cells which can process and present tumour-derived antigens to promote an effector T-cell response.



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HERPETIC INFECTION INCLUDING DISSEMINATED HERPETIC INFECTIONS

Herpetic infections including but not limited to cold sores and herpes keratitis have been reported in patients treated with IMLYGIC®. Patients who develop herpetic infections should be advised to follow standard hygiene practices to prevent viral transmission.

Disseminated herpetic infection, including serious cases of disseminated herpetic infection, have been reported in patients treated with IMLYGIC®.

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

IMLYGIC® is **contraindicated in severely immunocompromised individuals**. Based on animal data, patients who are severely immunocompromised (patients with any severe congenital or acquired cellular and/or humoral immune deficiency) are at risk of developing life-threatening disseminated herpetic infection and should not be treated with IMLYGIC®.

- Consider the risks and benefits of treatment before administering IMLYGIC® to immunocompromised patients e.g. those with:
  - HIV/AIDS
  - leukaemia, lymphoma
  - common variable immunodeficiency
  - those who require chronic high dose steroids or other immunosuppressive agents (e.g. chemotherapy)
- Immunocompromised healthcare professionals, including pregnant women, **should not prepare or administer IMLYGIC®.**
- Close contacts who are immunocompromised should not change the patient's dressings or clean their injection sites.

ACCIDENTAL EXPOSURE AND TRANSMISSION OF IMLYGIC® TO HEALTHCARE PROFESSIONALS

Accidental exposure to IMLYGIC® may lead to transmission of IMLYGIC® and herpetic infection. It is important to follow the precautions below to avoid accidental exposure to IMLYGIC®.

- Always wear protective gown or laboratory coat, safety glasses and gloves while preparing or administering IMLYGIC®.
- Cover any exposed wounds before handling IMLYGIC®.
- Avoid contact with skin, eyes, or mucous membranes.
- Avoid ungloved direct contact with injected lesions or body fluids of treated patients.
- Accidental needle-stick and splash-back into eyes or mouth have been reported in healthcare professionals during preparation and administration of IMLYGIC®.
- In the event of accidental exposure 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, exposed individuals should be advised to clean the affected area thoroughly with soap and water and/or a disinfectant.
- IMLYGIC® is sensitive to acyclovir.

ACCIDENTAL EXPOSURE AND TRANSMISSION OF IMLYGIC® TO CLOSE CONTACTS

Accidental exposure to IMLYGIC® may lead to transmission of IMLYGIC® and herpetic infection. The following precautions should be followed to avoid accidental exposure and prevent transmission of IMLYGIC® to close contacts (household members, caregivers, sex partners, or someone the patient shares a bed with) of treated patients:

- After administration, change gloves prior to applying occlusive dressings to injected lesions. Wipe the exterior of occlusive dressing with an alcohol wipe. Advise patients to keep the injection sites covered with airtight and watertight dressings at all times, if possible. To minimise the risk of viral transmission, patients should keep their injection sites covered for at least 8 days from the last treatment visit or longer if the injection site is weeping or oozing. Patients should be advised to keep the dressing on until the weeping or oozing resolves. Advise patients to apply the dressing as instructed by their healthcare provider and to replace the dressing if it falls off.

- Patients should be advised to follow standard hygiene practices to prevent viral transmission to close contacts.
- Close contacts should avoid direct contact with injected lesions or body fluids of treated patients.
  - The treated patient should minimise the risk of exposure of blood and body fluids to close contacts for the duration of IMLYGIC® treatment, and **through 30 days after the last administration of IMLYGIC®.** The following activities should be avoided:
    - Sexual intercourse without a latex condom
    - Kissing if either party has an open mouth sore
    - Common usage of cutlery, crockery, and drinking vessels
    - Common usage of injection needles, razorblades, and toothbrushes
- 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.
  - 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 as household waste.
- If close contacts come in contact with the injection site or body fluids they should be advised to clean the affected area thoroughly with soap and water and/or a disinfectant. If signs or symptoms of herpetic infection develop, they should contact their healthcare professional.
- IMLYGIC® is sensitive to acyclovir.

SUSPECTED HERPETIC LESIONS

For suspected herpetic lesions, a laboratory test may be performed at the discretion of the treating physician for a polymerase chain reaction (PCR) test for DNA specific to IMLYGIC®.

For further information on testing of suspected herpetic lesions, please contact the local Amgen representative at 01223 436441 or by email to gbinfoline@amgen.com.

PREGNANCY

- Adequate and well controlled studies have not been conducted in pregnant women.
- No effects on embryo-foetal development have been reported in animal studies.
- IMLYGIC® should **not be used during pregnancy** unless the potential benefit to the patient justifies the potential risk to the unborn baby.
- Wild-type herpes simplex virus type-1 (HSV-1) infection in the mother has been associated with life-threatening or fatal disseminated herpetic infection in the foetus or neonate in pregnancy or during birth due to viral shedding. There could be a **risk to the foetus or neonate** if IMLYGIC® were to act in the same manner.
- Transplacental metastases of malignant melanoma can occur. As IMLYGIC® is designed to enter and replicate in the tumour tissue, there could be a risk of foetal exposure to IMLYGIC® from tumour tissue that has crossed the placenta.
- Women of childbearing potential should be advised to use an effective method of **contraception to prevent pregnancy** during treatment with IMLYGIC®.
- Advise patients of the potential hazards to the foetus and/or neonate if IMLYGIC® is used during pregnancy, or if the patient becomes pregnant while taking IMLYGIC®.

IMPORTANT ACCOMPANYING PATIENT EDUCATIONAL MATERIALS

Please review the following important safety information with your patients **every time** you administer IMLYGIC®:

- Package Leaflet – includes important safety information for patients receiving IMLYGIC®.
- Patient Safety Brochure – a brief summary of the risks of accidental exposure and transmission of IMLYGIC®, **risk in patients with a weakened immune system,** measures for safe use and prevention of accidental exposure, and what to do if a close contact is accidentally exposed to IMLYGIC®.
- Please ensure the patients receive the completed **Patient Alert Card** with the first administration of IMLYGIC®. Patients should be instructed to carry the Patient Alert Card with them at all times and present it to healthcare professionals upon consultation or hospitalisation.
- Record the batch number for every administration of IMLYGIC® on the Patient Alert Card. If at one of the subsequent IMLYGIC® administrations, the patient has lost or forgotten to bring the Patient Alert Card, please supply a new one.

Provide each patient with a Package Leaflet, Patient Safety Brochure and Patient Alert Card every time you administer IMLYGIC® to the patient as the information may change over time. Should you require additional copies of the educational materials (Information for Physicians, Patient Safety Brochure, Patient Alert Card), please contact Amgen Medical Information on 01223 436441 or by email to gbinfoline@amgen.com.

REPORTING OF SUSPECTED ADVERSE REACTIONS AND CASES OF PREGNANCIES

IMLYGIC® is classified as an Advanced Therapy Medicinal Product, and therefore you are requested to provide the manufacturing batch number when reporting suspected adverse reactions or cases of pregnancies.

- Please ensure the batch number of ***each injection*** administered is clearly documented in the respective patient's medical records.
- Always provide the batch number from the patient's record when reporting suspected adverse reactions or cases of pregnancies.

Adverse reactions/events should be reported to the Health Products Regulatory Authority (HPRA) using the available methods via www.hpra.ie. Adverse reactions/events should also be reported to Amgen Limited on +44 (0)1223 436441 or Freephone 1800 535 160.

PLEASE PROVIDE THE BATCH NUMBER OF THE ADMINISTERED VIAL WHEN REPORTING.
See section 4.8 of the SmPC for information on the reporting of suspected adverse reactions.

PLEASE REFER TO THE CURRENT SUMMARY OF PRODUCT CHARACTERISTICS (SMPC) FOR IMLYGIC® PROVIDED WITH THIS BROCHURE AND AVAILABLE ONLINE AT HTTPS://WWW.MEDICINES.IE/.

PLEASE REFER TO HTTPS://WWW.MEDICINES.IE/ FOR CURRENT VERSION OF PACKAGE LEAFLET.

SHOULD YOU HAVE ANY QUESTIONS OR REQUIRE ADDITIONAL INFORMATION REGARDING THE USE OF IMLYGIC®, PLEASE CONTACT AMGEN MEDICAL INFORMATION ON +44 (0) 1223 436441 OR BY EMAIL TO GBINFOLINE@AMGEN.COM.