Product: IMLYGIC

Proper Name: talimogene laherparepvec

Manufacturer: Amgen Inc.

Indication: Indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Description: IMLYGIC was derived from a novel primary HSV-1 isolate (JS1, ECACC Accession Number 01010209) that demonstrates enhanced oncolytic activity towards tumor cells, as compared to the commonly used laboratory strains (e.g., 17syn+).

BLA: STN 125518

Regulatory Milestone:

DATE	MILESTONES
June, 2002	First subject enrolled in BioVex Study 001-01 in the United Kingdom
May 2005	US IND 12412 active (sponsor BioVex)
April 2008	FDA Special Protocol Assessment granted for Phase 3 Study 005/05
April 2009	First subject enrolled in Study 005/05
January 2011	Fast Track designation granted
March 2011	Orphan drug designation granted
December 2012	Data cut-off for primary endpoint for Study 005/05
October 2013	Pre-BLA Meeting
July 2014	Final BLA Module 5 (clinical) submitted
September 2014	Standard BLA review timeline (10 months)

November 2014	BLA major CMC amendment submitted
April 29, 2015	FDA Advisory Committee meeting

PDUFA Goal Date: October 27, 2015

FDA approval date: October 27, 2015

EMA approval date: December 16, 2015

TGA approval date: December 21, 2015

Package Insert: Package Insert - IMLYGIC

Summary Basis for Regulatory Approval: October 27, 2015 Summary Basis for Regulatory Action - IMLYGIC

European Public Assessment Report: October 22, 2015 Assessment report - IMLYGIC

Manufacturing Platform:

PARAMETER	DATA	REFERENCE
Manufacturer	Amgen Inc.	
Transgene	hGM-CSF Gene	1
Indication	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.	1
Virus & Serotype	Wild-type HSV-1 genome (new isolate JS1)	2
Cell Substrate	African green monkey kidney cells (Vero)	3

Manufacturing platform	The active substance manufacturing process includes cell expansion, virus infection and production (in roller bottles), harvest, recovery, and purification stages. The purification process consists of endonuclease digestion, clarification by filtration, ultrafiltration/diafiltration (UF/DF), two chromatography steps (IEX, SEC) and a final sterile filtration to produce the active substance. No additional filtration occurs beyond this step-in drug product manufacture. The sterile filtration step therefore provides the terminal sterile filtration for the drug product.	3
Dose in vial/final container	106 (1 million) PFU per mL, 108 (100 million) PFU per mL in single-use vials	1
Dose / patient	Starting dose is up to a maximum of 4 mL of IMLYGIC at a concentration of 106 (1 million) plaque-forming units (PFU) per mL. Subsequent doses should be administered up to 4 mL of IMLYGIC at a concentration of 108 (100 million) PFU per mL.	1

1. Package insert: Package Insert - IMLYGIC
2. EPAR full: IMLYGIC
3. EPAR quality: October 22, 2015 Assessment report - IMLYGIC (page)
4. FDA SBAR – quality: October 27, 2015 Summary Basis for Regulatory Action - IMLYGIC

Advisory Committee:

A joint meeting of CBER's Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) and CDER's Oncologic Drugs Advisory Committee (ODAC) was held on April 29, 2015 in order to provide advice to FDA regarding safety, dosing, and an overall benefit-risk assessment for IMLYGIC. There was extensive discussion, with no clear consensus, regarding whether the efficacy of IMLYGIC was limited to a definable subset of the Study 005 population (e.g., those subjects with less advanced disease). The committee voted 22 to 1 (Yes to No) to the

question, "does talimogene laherparepvec have an overall favorable benefit-risk profile to support traditional approval for the treatment of injectable, regionally or distantly metastatic melanoma?"

Safety: Not available

Clinical Trials:

NCT	TRIAL PHASE	SUBJECTS ENROLLED	STUDY TITLE	COUNTRIES
NCT00769704	3	437	Efficacy and Safety Study of Talimogene Laherparepvec Compared to Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) in Melanoma	United States, Canada, South Africa, United Kingdom
NCT01368276	3	31	An Extended Use Study of Safety and Efficacy of Talimogene Laherparepvec in Melanoma	United States
NCT00289016	2	50	A Study of Talimogene Laherparepvec in Stage IIIc and Stage IV Malignant Melanoma	United States, United Kingdom
NCT02574260	2	3	An Extension Protocol for the Extended Use of Talimogene Laherparepvec for Eligible Patients Who Participated in Study 002/03 (NCT00289016)	

EudraCT Numbers:

- 2018-002165-19
- 2015-003011-38
- 2014-000185-22
- 2015-003196-29
- 2019-004403-12
- 2013-005552-15
- 2019-001906-61
- 2012-000307-32
- 2018-002677-22
- 2015-003645-25
- 2014-005386-67
- 2019-001911-22

Publications:

- MedlinePlus Drug Information: Talimogene Laherparepvec Injection
- Melanoma Treatment (PDQ®) - PDQ Cancer Information Summaries - NCBI Bookshelf
- Dictionary of Cancer Terms - PDQ Cancer Information Summaries - NCBI Bookshelf
- Wald, A., Benedetti, J., Davis, G., Remington, M., Winter, C., & Corey, L. (1994). A randomized, double-blind, comparative trial comparing high- and standard-dose oral acyclovir for first-episode genital herpes infections. Antimicrobial agents and chemotherapy, 38(2), 174–176. https://doi.org/10.1128/aac.38.2.174
- Puzanov, I., Milhem, M. M., Minor, D., Hamid, O., Li, A., Chen, L., Chastain, M., Gorski, K. S., Anderson, A., Chou, J., Kaufman, H. L., & Andtbacka, R. H. (2016). Talimogene Laherparepvec in Combination with Ipilimumab in Previously Untreated, Unresectable Stage IIIB-IV Melanoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, 34(22), 2619–2626. https://doi.org/10.1200/JCO.2016.67.1529
- Andtbacka, R. H., Ross, M., Puzanov, I., Milhem, M., Collichio, F., Delman, K. A., Amatruda, T., Zager, J. S., Cranmer, L., Hsueh, E., Chen, L., Shilkrut, M., & Kaufman, H. L. (2016). Patterns of Clinical Response with Talimogene Laherparepvec (T-VEC) in Patients with Melanoma Treated in the OPTiM Phase III Clinical Trial. Annals of surgical oncology, 23(13), 4169–4177. https://doi.org/10.1245/s10434-016-5286-0
- Andtbacka, R. H., Agarwala, S. S., Ollila, D. W., Hallmeyer, S., Milhem, M., Amatruda, T., Nemunaitis, J. J., Harrington, K. J., Chen, L., Shilkrut, M., Ross, M., & Kaufman, H. L. (2016). Cutaneous head and neck melanoma in OPTiM, a randomized phase 3 trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor for the treatment of unresected stage IIIB/IIIC/IV melanoma. Head & neck, 38(12), 1752–1758. https://doi.org/10.1002/hed.24522
- Seery V. (2017). Intralesional Therapy: Consensus Statements for Best Practices in Administration from the Melanoma Nursing Initiative℠. Clinical journal of oncology nursing, 21(4 Suppl), 76–86. https://doi.org/10.1188/17.CJON.S4.76-86
- Ribas, A., Dummer, R., Puzanov, I., VanderWalde, A., Andtbacka, R., Michielin, O., Olszanski, A. J., Malvehy, J., Cebon, J., Fernandez, E., Kirkwood, J. M., Gajewski, T. F., Chen, L., Gorski, K. S., Anderson, A. A., Diede, S. J., Lassman, M. E., Gansert, J., Hodi, F. S., & Long, G. V. (2017). Oncolytic Virotherapy Promotes Intratumoral T Cell

Infiltration and Improves Anti-PD-1 Immunotherapy. Cell, 170(6), 1109–1119.e10. https://doi.org/10.1016/j.cell.2017.08.027

- Kaufman, H. L., Andtbacka, R., Collichio, F. A., Wolf, M., Zhao, Z., Shilkrut, M., Puzanov, I., & Ross, M. (2017). Durable response rate as an endpoint in cancer immunotherapy: insights from oncolytic virus clinical trials. Journal for immunotherapy of cancer, 5(1), 72. https://doi.org/10.1186/s40425-017-0276-8
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- Andtbacka, R., Collichio, F., Harrington, K. J., Middleton, M. R., Downey, G., Öhrling, K., & Kaufman, H. L. (2019). Final analyses of OPTiM: a randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III-IV melanoma. Journal for immunotherapy of cancer, 7(1), 145. https://doi.org/10.1186/s40425-019-0623-z
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