CBER Clinical Reviewer Memo: Regulatory Approval Action

Application Type	Original Application
STN	125518/0
Reviewer Name	Maura C. O'Leary, MD
Date	October 8, 2015
Applicant	Amgen, Inc.
Established Name	talimogene laherparepvec
(Proposed) Trade Name	IMLYGIC
Pharmacologic Class	Oncolytic immunotherapy
Indication and Intended Population(s) per Applicant	Treatment of injectable regionally or distantly metastatic melanoma.

Recommendation on Regulatory Action:

Traditional Approval: IMLYGIC (talimogene laherparepvec) is a genetically modified oncolytic viral therapy indicated for the local treatment of cutaneous, subcutaneous and nodal lesions in patients with unresectable recurrent melanoma. IMLYGIC has not been shown to improve overall survival or have an effect on visceral lesions.

Justification for Traditional Approval:

The clinical BLA review (Bross, Le, O'Leary, October 2015) recommends approval based on the Accelerated Approval pathway [(Subpart E (21 CFR601.41)] and views the durable response as a surrogate for clinical benefit. This memo is to recommend traditional approval [21 CRF 312.84, 21 CFR 314.126 and 21 CFR 601. 25] for IMLYGIC (talimogene laherparepvec). This recommendation is based on the following:

Primary Endpoint:

- The primary endpoint was durable response rate (DRR), defined as the percentage of subjects with complete response (CR) or partial response (PR) maintained continuously for at least 6 months from the time the response was first observed within 12 months of starting therapy based on World Health Organization (WHO) response criteria utilizing an independent Endpoint Assessment Committee (EAC) which was blinded to subjects' treatment allocation. The 005/05 study met its primary endpoint of durable response rate (DRR) for complete responders and partial responders that lasted a minimum of 6 months compared to control (granulocyte-macrophage colony-stimulating factor [GM-CSF]): 16.3% (48/295) versus 2.1% (3/141) $p < 0.0001$ per the FDA review.

Clinical Benefit:

- The durable response rate of CR and PR for a minimum of six months represents a direct clinical benefit as demonstrated by the improvement and/or disappearance of local and regional cutaneous, subcutaneous, and nodal lesions. In addition, it was noted in the photographs of the durable responders (36 of 46) to IMLYGIC that were

used to assess the lesion size and response, that the subjects achieved a cosmetic improvement in 29 of 36 subjects whose photographs were available for review.

- Three durable responders were made surgically resectable. All subjects on the trial were unresectable at entry. To enable definitive surgery for local or regional disease is a direct clinical benefit.

Clinical effectiveness:

- The FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products states that more than one trial is usually recommended to provide the independent substantiation of the results, for the assessment of effectiveness. However, the added rigor and size of contemporary clinical trials have made it possible to rely on a single adequate and well-controlled study. The Study 005/05 met its primary endpoint of durable response rate of CR and PR for a minimum of six months in the ITT population with a highly significant p value of 0.0001.
- To conduct a second trial of IMLYGIC versus placebo or other control is not feasible. An add-on trial with another licensed agent for recurrent and metastatic melanoma may not be interpretable with respect to the effectiveness of IMLYGIC alone.

Benefit/Risk:

- The primary review (Bross, Le, O'Leary; August, 2015), describes the safety profile for IMYLGIC. No safety signals were identified.
- There is a concern that health care providers might prescribe IMYLGIC alone for the treatment of advanced stage melanoma with visceral disease when there are available treatments that have demonstrated a survival advantage. IMYLGIC does not have a survival advantage nor has IMYLGIC demonstrated the ability to improvement in visceral disease in advanced stage melanoma.
- The benefits (durable response, achieve surgical resectability) as detailed above are sufficient to justify traditional approval for IMYLGIC in the local treatment of cutaneous, subcutaneous and nodal lesions in patients with unresectable recurrent melanoma.