MEMORANDUM

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FDA / CBER / OCTGT / DCEPT

BLA 125518	
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Review date	October 23, 2015
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Pharm / Tox Reviewer	Ying Huang, Ph.D.
Clinical Reviewers / Team Leader	Robert Q. Le, M.D., Ph.D.; Maura C. O'Leary, M.D. / Peter Bross, M.D.
Statistical Reviewer / Team Leader	Yuqun Abigail Luo, Ph.D. / Shiowjen Lee, Ph.D.
Pharmacovigilance Reviewer	Meghna Alimchandani, M.D.
Regulatory Project Manager	Mark Davidson
Sponsor	Amgen, Inc.
Product	talimogene laherparepvec
Proposed Indication	Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
Recommendation	Approval

Please see the primary clinical review by Drs. Le, O'Leary, and Bross, the additional review memo by Dr. O'Leary, the statistical review by Dr. Luo, the pharmacovigilance review by Dr. Alimchandani, and the pharmacology/toxicology review by Dr. Huang for details of this submission. The clinical review team recommends approval of the biologics license application (BLA). I agree with that recommendation, and with the post-marketing pharmacovigilance plan as outlined in Dr. Alimchandani's review.

The purpose of this memo is to present my perspective on the rationale for the BLA approval, particularly regarding the issue of regular (traditional) approval versus Accelerated Approval.

1) Regular (traditional) approval vs. Accelerated Approval

There has been substantial discussion within the review team regarding the clinical meaningfulness of durable response rate (DRR) and the regulatory pathway for approval. Some members of the review team do not accept DRR as clinically meaningful, but consider DRR as a surrogate endpoint reasonably likely to predict a clinical benefit, such as prolongation of overall survival. Therefore, some members of the review team have recommended Accelerated Approval for talimogene laherparepvec (IMLYGIC), with a requirement that Amgen conduct another clinical trial to confirm the benefit of IMLYGIC.

However, other members of the review team accept DRR as clinically meaningful, particularly in consideration of statements during the Advisory Committee meeting. At the Advisory Committee meeting, patients and their caregivers spoke of the value, both cosmetic and psychological, of watching their skin lesions disappear. This perspective was supported by a few cases in which photographs provided evidence of dramatic effects on skin lesions. As noted in Dr. O'Leary's memo, there were also a few Study 005 subjects who had the benefit of having their unresectable lesions become resectable. There may not be metrics that adequately capture the value of watching a tumor disappear, but I was persuaded by the patients, their caregivers, and the physicians who served on the Advisory Committee that DRR is clinically meaningful. In addition, the Advisory Committee voted strongly (22-1) in favor of regular approval. Therefore, the DRR endpoint is sufficient for regular approval, so that the Accelerated Approval pathway is not necessary for this BLA.

2) Substantial evidence of effectiveness:

One issue is whether Study 005 meets the regulatory standard for a single trial to provide the primary evidence of effectiveness to support marketing approval. The FDA Guidance on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998) states that "… reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." Study 005 does not provide substantial evidence of a clinically meaningful effect on such an outcome measure, and it is conceivable that a confirmatory trial could be conducted. However, the available treatments and clinical management for melanoma have changed substantially since Study 005 was conducted. As a result of these changes, it would not be feasible for a second trial to provide data that substantially refutes the Study 005 conclusion of an effect on DRR in patients with advanced melanoma. Thus, due to the relatively unique circumstances involving the changes in practice since Study 005 was conducted, the data available at this time provide the substantial evidence necessary for BLA approval.

3) Benefit - Risk assessment

BLA approval requires not just substantial evidence of effectiveness, but also an

overall favorable benefit-risk assessment. As noted in both the clinical review and Dr. O'Leary's memo, the risks of IMLYGIC are primarily mild, transient, and manageable. The risk of shedding, including the risk of transmission of infection to close contacts and healthcare providers, will be assessed in a postmarketing study and a postmarketing clinical trial. Although patients with advanced melanoma have a life-threatening disease, and IMLYGIC has not been shown to have an effect on survival, the benefits of IMLYGIC are clinically meaningful and may be important for some patients. These benefits are sufficient to justify the risks of IMLYGIC, which can be mitigated through postmarketing assessments and labeling, as described below. Therefore, IMLYGIC has an overall favorable benefit-risk profile for some patients with melanoma.

4) Indication statement and labeling issues

Subgroup analyses of the Study 005/05 data suggest that the benefit of IMLYGIC might be greater in, or occur only in, patients with less advanced melanoma. Some members of the review team, along with some members of the Advisory Committee, proposed that the indicated population should be limited to patients with less advanced disease. However, other Advisory Committee members advocated for a broader indicated population, and the Advisory Committee did not reach a consensus on this issue. Considering the deliberations of the Advisory Committee, and that subgroup analyses should be interpreted with caution, the indicated population should not be limited to patients with less advanced disease.

One of the greatest concerns with approval of IMLYGIC is that patients will receive IMLYGIC instead of a product with a proven benefit on overall survival. This indirect risk has been mitigated by labeling that 1) states that IMLYGIC is for the treatment of lesions, not for the treatment of melanoma, and 2) includes a limitation of use that states that IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases. The direct risks of IMLYGIC administration, as described in the labeling, are mostly mild and moderate adverse events (fatigue, chills, pyrexia, nausea influenza-like illness, and injection-site pain) that resolve within 72 hours. The most common serious adverse event is cellulitis, which is readily treatable. These risks of IMLYGIC are further mitigated by the *Contraindications* (pregnancy; immunocompromised patients) and the *Warnings and Precautions* in the labeling.

The labeling states that IMLYGIC is indicated for treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. This indication statement reflects the population in Study 005, and does not limit the indicated population to patients with a particular stage of metastatic melanoma. The labeling must adequately describe the benefits and risks of IMLYGIC so that providers and their patients can make well-informed decisions regarding each patient's care. Ultimately, patients and healthcare providers will decide which individual patients have clinical situations for which IMLYGIC offers an overall favorable balance of benefits and risks. This assessment will be highly individualized, following consideration of the benefits and risks of other available treatments for melanoma. Thus, the exact role of IMLYGIC in the armamentarium of treatments for patients with melanoma will be determined with time and experience in the marketplace.

Summary

DRR is clinically meaningful; the BLA provides substantial evidence of effectiveness; and, with appropriate labeling and required postmarketing assessments, there is a favorable overall balance of benefits and risks for the proposed indicated population. Therefore, the BLA is sufficient to support regular approval.

Recommendations

1) Regular approval of IMLYGIC for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery

2) Labeling should include a limitation of use statement that IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

3) Pharmacovigilance postmarketing requirements, as described in the Pharmacovigilance review