…..May 2022

Imlygic® (talimogene laherparepvec): Special Considerations to Minimize the Potential Occurrence of Adverse Events in HSV-1 Seronegative Patients Receiving Vials From Affected Lots: Injections from Imlygic 106 PFU/mL vials from the affected lot numbers should be administered "as soon as practically feasible" and no later than 18 hours after thaw and storage at 2°C to 8°C.

Dear Healthcare Professional,

Amgen in agreement with the European Medicines Agency would like to inform you of the following:

Summary

- Imlygic 10^6 PFU/mL vials from the lots listed in Annex 1 below may have a lower than the expected level of virus infectivity if they were thawed and subsequently stored at 2°C to 8°C for 18 or more hours prior to administration.
- HSV-1 seronegative patients who have received injections from vials from the affected lots and administered later than 18 hours after thaw and storage at 2°C to 8°C may potentially be at risk for an increased incidence of severe and/or serious adverse events, most likely following the second dose of Imlygic (with 10^8 PFU/mL dose concentration).
- Your site has received in the past Imlygic 10^6 PFU/mL vials from the affected lots listed below

Background on the safety concern

Imlygic® is oncolytic immunotherapy 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.

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

Imlygic® is thawed at room temperature until liquid. The time to achieve a complete vial thaw is expected to be approximately 30 minutes, depending on room temperature. The label indicates that Imlygic® may be thawed and subsequently stored for up to 24 hours at 2°C to 8°C prior to administration. However, the affected lots listed below may have a lower than expected level of virus infectivity if they were thawed and subsequently stored at 2°C to 8°C for 18 or more hours prior to administration.

As a result, ***Imlygic® from the lots listed in the Annex 1 is to be administered "as soon as practically feasible" and no later than 18 hours after thaw and storage at 2°C to 8°C.***

In phase 1 Clinical Trial, ascending-dose study of Imlygic, subjects who were HSV-1 seronegative at clinical study entry experienced more adverse events than subjects that were HSV-1 seropositive. The adverse events consisted primarily of flu-like symptoms. Symptoms were mitigated using a dosing regimen that included an initial lower dose concentration of 10^6 PFU/mL in all subjects followed by subsequent dose concentration of 10^8 PFU/mL, regardless of HSV-1 serostatus. Therefore, this letter is provided to make sure the proper viral load necessary for HSV-1 seroconversion is delivered at the initial dose to help mitigate the

potential risk for an increased incidence of severe and/or serious drug adverse events following the subsequent dose with a dose concentration of 10^8 PFU/mL.

Call for reporting

Healthcare providers are encouraged to report adverse events, especially in HSV-1 seronegative patients who received previously Imlygic® with an initial dose concentration of 10^6 PFU/mL from a vial with the less active product (less viral infectivity) according to national reporting requirements. In order to establish a relationship with the initial dose, reference should be made to the possibly reduced viral infectivity of the initial dose as well as its lot number. < Details of the national reporting system to be included >

Company contact point

Should you have any questions or require additional information regarding the use of Imlygic®, please contact Amgen's local representative [insert local contact details].

Annex 1

List of affected lots:

Lot numbers			
1106660	1106685	1107011	1108903
1109673	1110758	1110759	1110762
1112262	1114340	1120632	1123798
1123929	1125937	1113086	1113944
1116789	1118707	1119867	1122132
1123802	1079890AB	1108670	1109329
1111656	1120746	1123155	1121895

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	*Imlygic® - talimogene laherparepvec 10^6 PFU/mL*
Marketing authorisation holder(s)	*Amgen Europe B.V.* *Minervum 7061, 4817 ZK Breda* *The Netherlands*
Safety concern and purpose of the communication	*QD2022-087/H/Imlygic/Defective Product Report:* *Special Considerations to Minimize the Potential Occurrence of Adverse Events in HSV-1 Seronegative Patients Receiving Vials From Affected Lots.*
DHPC recipients	*Qualified physicians experienced in the treatment of cancer, pharmacists, hospital pharmacists and nurses working at the sites that received impacted vials and for which it seems possible/likely that doses still remain unused.*
Member States where the DHPC will be distributed	*Austria, Germany, Finland, the Netherlands, Sweden and Luxemburg. DHPC will also be distributed to Norway*

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP/CMDh	19 May 2022
Submission of translated DHPCs to the national competent authorities for review	5 business days later
Agreement of translations by national competent authorities	10 business days later
Dissemination of DHPC	5 business days later