AMGEN

Thank and disclose to ID.

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Senior Coroner Andrew Harris
Inner South District Greater London,
Southwark Coroner's Court,
1 Tennis Street,
Southwark
SE1 1YD

1st July 2019

Re: Prevent Future Deaths Report for EH ('Report')
Date of Death (05.02.2018) (Case Ref: 00395-2018)

Dear Senior Coroner Harris,

Thank you for your Report dated 10th May 2019 to which we respond in accordance with the required timeline of 2nd July 2019. The incident, which is the subject of your Report, was brought to our attention by University College London, the Sponsor of the Cardamon Study ('Study'), as part of its standard safety reporting obligations to Amgen Limited ('Amgen'), the marketing authorization holder (MAH) of the study drug, Kyprolis® (carfilzomib), on 12th February 2018.

We refer to Section 5.2 of your Report which seeks our response in relation to the following concern:

"The expert pharmaceutical physician gave a recommendation that the need for cardiac monitoring was made more definitive in the drug prescribing information for Carfilzomib (and possibly others) which was prescribed in the Cardamon Trial."

We take all adverse event ('AE') reporting very seriously at Amgen. Governance processes, both internally at Amgen and at European Medicines Agency ('EMA') and Pharmacovigilance Risk Assessment Committee ('PRAC') level, mandate that AE data, such as in this case, is evaluated on a regular basis to establish the benefit risk profile of authorised medicinal products and determine whether adjustments are needed in the Summary of Product Characteristics ('SmPC') and Patient Information Leaflet ('PIL'). The labeling process in the EU is a collaboration between the agency (EMA/PRAC) and the MAH. A unilateral update to the SmPC based on one case alone, would not therefore be possible as examination of extensive medical evidence by all stakeholders would be required prior to any SmPC change being implemented.

The current SmPC for Kyprolis lists cardiac failure and myocardial ischaemia as common side effects and myocardial infarction as an uncommon side effect in section 4.8 and contains 'special warnings and precautions for use' for patients both with and without pre-existing cardiac conditions in Section 4.4:

"New or worsening cardiac failure (e.g. congestive cardiac failure, pulmonary oedema, decreased ejection fraction), myocardial ischaemia and infarction have occurred following administration of Kyprolis. Death due to cardiac arrest has occurred within a day of Kyprolis administration and fatal outcomes have been reported with cardiac failure and myocardial infarction".

The SmPC warns that an increased risk of cardiac failure exists in patients with a medical history of cardiac disorder, the elderly and patients of Asian ethnicity, further, that patients with signs or symptoms of NYHA Class III or IV cardiac failure, recent history of myocardial infarction, uncontrolled angina or arrhythmias ***"should be treated with caution and remain under close follow-up."*** The Patient Information Leaflet ('PIL') for Kyprolis (A2), which contains in lay terms the same warnings, precautions and side effect information, states at section 2 ***"Your doctor will examine you and review your full medical history. You will be monitored closely during treatment"*** and continues to specifically warn patients to talk to their doctor about any existing heart problems in case additional tests are required prior to taking Kyprolis. There are no warnings or recommendations in the SmPC or PIL for patients without a history of cardiac disorder.

As Amgen was not the Sponsor of the Study, we do not have sufficient information to determine whether the patient had cardiac history at time of enrollment, or not.

We therefore consider that cardiac monitoring guidance is already definitively outlined in the prescribing information for Kyprolis. As the guidance provided in the current SmPC has been approved by PRAC and EMA, we believe that no further revisions to the SmPC are required. We will however, continue to conduct ongoing pharmacovigilance of Kyprolis and to evaluate our SmPC guidance on cardiac monitoring, in accordance with all pharmacovigilance requirements.

We trust that this information will serve to resolve your concern and bring this matter to a close, but please do not hesitate to contact us if we can be of any further assistance.

Yours sincerely,

[redacted]

[redacted]
Medical Director, UK & Ireland