Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for carboplatin, the scientific conclusions are as follows:

The Kounis syndrome is defined as any allergy-mediated acute coronary syndrome, including stent thrombosis resulting from anaphylactoid processes, therefore could be considered as a coronary syndrome in the setting of allergic/anaphylactic reactions. The clinical manifestations of this syndrome are always associated with subclinical, clinical, acute or chronic allergic reactions accompanied by cardiac symptomatology.

Cumulatively 8 cases have been selected from the cases presented by the marketing authorisation holders (MAHs) in their review (also confirmed from a query conducted in Eudravigilance database) and were considered supportive of Kounis syndrome and carboplatin.

Of the 8 cases, 5 cases of coronary artery vasospasm induced by carboplatin were retrieved from case reports documented in published literature. In particular, two cases reporting the preferred term (PT) "Kounis Syndrome", one case with PT "Arteriospasm coronary" and two cases with PT "Angina pectoris associated with hypersensitivity reaction". Among these literature cases, two (*Baroni M, et al. Journal of Cardiology Cases 4: e58-e61, No. 1, Aug 2011; Tambe V et al. American Journal of Therapeutics. /Nov/2020; 27*) were well described and provided evidence of possible causal association between Kounis syndrome and carboplatin with ECG suggestive of acute coronary syndrome. One case (*Martin R. et al. Cancer Chemother. Pharmacol. 2002;50:429-431*) was described as confounded by multi-drug therapy and another (*Mark A. et al., American Journal of Obstetrics and Gynecology*) presented no data on ECG. Nevertheless, both cases were considered possible Kounis syndrome related to carboplatin based on temporal relationship and diagnostic criteria. In the fifth case (*Shuichi Y et al. Journal of Japanese Circulation Journal, 1996, vol 1996, Pgs 185-188*), with fatal outcome, etoposide was reported as confounding factor. However, the authors described a temporal relationship with carboplatin and diagnostic criteria plausible with Kounis syndrome.

The remaining three cases were received from healthcare professionals. These three cases less documented are considered as having a contributory value in this review.

Overall, in seven cases the patients experienced cardiac symptoms in a context of hypersensitivity/anaphylaxis with a temporal relationship compatible with a diagnosis of Kounis syndrome, which was also supported by ECG findings (ST segment elevation documented in 5 cases). Information about findings from myocardial perfusion imaging, cardiac enzymes and coronary angiography were not systematically reported.

For the majority of the cases, the events resolved following the treatment with nitroglycerine and/or corticosteroids.

Allergic reactions/hypersensitivity are already listed as ADR and important identified risk for carboplatin. Moreover, articles regarding antineoplastic and cardiotoxicity document that platinum-agents, such as cisplatin, carboplatin and oxaliplatin, can induce Kounis syndrome, typically type I and/or type II variant.

Based on the review of spontaneous cases, the literature, and biological plausibility, it is concluded that there is reasonable evidence to suggest a causal relationship between exposure to carboplatin and the development of Kounis syndrome. Since hypersensitivity reactions linked to carboplatin therapy have been reported and patients with a pre–existing coronary disease or with risk factors for coronary disease are at higher risk of more severe Kounis syndrome with progression to myocardial infarction, it is considered important to inform the Healthcare professionals (HCPs) and patients about signs and symptoms requiring careful attention.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for carboplatin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing carboplatin is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing carboplatin are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**)

Summary of Product Characteristics

Section 4.4

A warning should be added as follows:

Hypersensitivity Reactions

[…]
There have been reports of hypersensitivity reactions which progressed to Kounis syndrome (acute allergic coronary arteriospasm that can result in myocardial infarction, see section 4.8).

Section 4.8 – Undesirable effetcs:

Cardiac disorders: Frequency 'Not known': **Kounis syndrome**

Package Leaflet:

Section 4 - Possible side effects

Allergic reactions

Tell your doctor immediately if you experience any of the following signs and symptoms that may indicate a serious allergic reaction ……. And **chest pain which can be a sign of a potentially serious allergic reaction called Kounis syndrome**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 November 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 January 2023