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:

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

Drug induced immune haemolytic anaemia (DIIHA) is a well-known complication reported for several platin salts. During the reporting period, haemolytic anaemia, with the presence of serologic drug-induced antibodies, has been reported in patients treated with carboplatin. In consideration of the fatal cases retrieved and the detection of carboplatin antibodies in the patients' samples suggesting a possible role in the development of haemolytic anaemia, it is deemed necessary to include a warning in the product information of carboplatin containing medicinal products to further inform about this risk.

Cases of acute promyelocytic leukaemia (APL) and myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments. Although most cases were confounded by administration of concomitant medication (e.g. etoposide, tegafur, cyclophosphamide, ifosfamide which are also known to induce secondary malignancies) and underlying malignant condition, a causal association between the occurrence of these events and carboplatin exposure could not be excluded. A warning to inform that such events have been observed should be inserted in the product information.

The evaluation of data on veno-occlusive disease collected during the reporting period, which included case reports, including fatal cases, and literature references, supports a possible causal association between the occurrence of veno-occlusive disease and carboplatin exposure due to the temporal relationship. It is considered that patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases.

Therefore, in view of the data presented in the reviewed PSURs, the PRAC considered that changes to the product information of medicinal products containing carboplatin, were warranted.

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

Grounds for the variation to the terms of the marketing authorisations

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 such marketing authorisations are varied accordingly.

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, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

[The following paragraphs should be inserted in this section:]

Hematologic toxicity

Hemolytic anemia with the presence of serologic drug-induced antibodies has been reported in patients treated with carboplatin. This event can be fatal.

[…]

Acute promyelocytic leukaemia and myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) have been reported years after therapy with carboplatin and other antineoplastic treatments.

[…]

Venoocclusive liver disease
Cases of hepatic venoocclusive disease (sinusoidal obstruction syndrome) have been reported, some of which were fatal. Patients should be monitored for signs and symptoms of abnormal liver function or portal hypertension which do not obviously result from liver metastases.

[…]

Tumour lysis syndrome (TLS)
In post marketing experience tumour lysis syndrome (TLS) has been reported in patients following the use of carboplatin alone or in combination with other chemotherapeutic agents. Patient at high risk of TLS, such as patients with high proliferative rate, high tumor burden, and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precaution taken.

[…]

- Section 4.8

[The following adverse drug reaction should be added under the SOC *Metabolism and Nutrition Disorders* with a frequency not known:]

Tumor lysis syndrome

Package Leaflet

- Section 2

[The following paragraphs should be inserted in this section:]

During treatment with carboplatin you will be given medicines which help reduce a potentially life-threatening complication known as tumour lysis syndrome, which is caused

by chemical disturbances in the blood due to the breakdown of dying cancer cells that release their content to the bloodstream.

- Section 4

Frequency not known*
- muscle cramping, muscle weakness, confusion, visual loss or disturbances, irregular heartbeat, kidney failure or abnormal blood test results (symptoms of tumor lysis syndrome which can be caused by the rapid breakdown of tumour cells) (see section 2).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position :	26 November 2016
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 January 2017

APPENDIX I

PRAC PSUR Assessment Report