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 oxaliplatin, the scientific conclusions are as follows:

Following a review of post-marketing cases, literature reports and observed imbalances of myocardial ischaemia and angina pectoris between treatment arms of clinical trials containing or not oxaliplatin, the weighted cumulative evidence is sufficient to support a causal association between oxaliplatin and acute coronary syndrome, including myocardial infarction and coronary arteriospasm. Similarly, the reference safety information for the platinum-based compound cisplatin includes severe coronary artery disease (CAD) as a listed term. However, the approved regimens of combination therapy for oxaliplatin include 5-FU and bevacizumab, which are also well known to be associated with cardiac ischaemia and myocardial infarction. In conclusion, the terms acute coronary syndrome including myocardial infarction, coronary arteriospasm and angina pectoris should be added to the oxaliplatin list of adverse drug reactions with a frequency unknown specifying that these have been observed in patients treated with oxaliplatin in combination with 5-FU or bevacizumab.

A number of cases of fall were reported in patients receiving oxaliplatin, some of which described as related to oxaliplatin. In clinical trials, the event of fall has been reported with a frequency very common (up to 2% depending on the regimen). The Product Information of oxaliplatin contains a number of terms which may lead to fall, such as anaemia, dizziness, peripheral sensory neuropathy, muscle weakness, visual disturbances etc. As a consequence, causality is highly probable. Moreover, the population exposed to oxaliplatin is often old and often frail. Careful attention should be paid to of the potential complications and injuries, involving falls, which could lead to impaired quality of life, life threatening condition or fatality in the elderly. In conclusion, fall should be added to list of adverse drug reactions with a frequency common.

Based on a number of post-marketing cases of oesophagitis with a close (1-10 days) temporal relationship with oxaliplatin administration, including 4 cases with short time to onset and no alternative explanation, the term oesophagitis should be added to the list of adverse drug reactions with a frequency unknown.

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 oxaliplatin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing oxaliplatin 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 oxaliplatin 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, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.8

The following adverse reaction(s) should be added under the SOC Cardiac disorders with a frequency unknown: Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with Oxaliplatin in combination with 5-FU and bevacizumab;

The following adverse reaction should be added under the SOC Injury, poisoning and procedural complications with a frequency common: Fall;

The following adverse reaction should be added under the SOC Gastrointestinal disorders with a frequency unknown: Oesophagitis.

Package Leaflet

· Possible side effects

The following adverse reactions should be added with a frequency unknown (frequency cannot be estimated from the available data):

Myocardial infarction (Heart attack), angina pectoris (pain or uncomfortable feeling in the chest)

Oesophageal inflammation (inflammation of the lining of the esophagus - the tube that connects your mouth with your stomach- resulting in pain and swallowing difficulty).

The following adverse reactions should be added with a frequency common:

Fall.

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of this position

Adoption of CMDh position:	December 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	26 January 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 March 2018