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 ipratropium/salbutamol, the scientific conclusions are as follows:

There were respectively 5 and 8 cases of lactic acidosis with salbutamol / ipratropium reported during the reporting period and cumulatively. As compensatory hyperventilation breathing is an important clinical sign in lactic acidosis which could be misinterpreted as a sign of asthma or chronic obstructive pulmonary disease (COPD) treatment failure, it is important to diagnose lactic acidosis developing during an acute exacerbation of bronchospasm either in severe asthma or COPD in order to avoid inappropriate intensification of ipratropium / salbutamol administration.

Based on the information presented in this PSUR, the PRAC considered that sections 4.4, 4.8 and 4.9 of the Summary of Product Characteristics should be amended to respectively add a warning on lactic acidosis, add lactic acidosis with a frequency unknown and provide details on the monitoring for lactic acidosis in case of overdose with salbutamol / ipratropium. The Package Leaflet is updated accordingly.

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 ipratropium/salbutamol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing ipratropium/salbutamol 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 ipratropium/salbutamol 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

A warning should be added as follows:

[…] **Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see Section 4.8 and 4.9). Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.** […]

- Section 4.8

The following adverse reaction(s) should be added under the SOC Metabolism and nutrition disorders with a frequency unknown:

Lactic acidosis (see section 4.4)

- Section 4.9

The section on overdose should be revised as follows:

[…] Any effects of overdosage are therefore likely to be related to the salbutamol component.

Manifestations of overdosage with salbutamol may include […].

Metabolic acidosis has also been observed with overdosage of salbutamol, including **lactic acidosis which has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.** […]

Package Leaflet

- Section 2 **What you need to know before you use [Product name]**

Warnings and precautions

[…]

A condition known as lactic acidosis has been reported in association with high therapeutic doses of salbutamol, mainly in patients being treated for an acute bronchospasm (see Section 3 and 4). Increase in lactate levels may lead to shortness of breath and hyperventilation even though there may be improvement in your wheezing. If you feel that

your medicine is not working as well as usual and you need to use the nebuliser more than your doctor has recommended, immediately talk to a doctor.
[...]

- Section 4

[...] The following side effects can also happen but the frequency of these are not known:
[...] **A condition known as lactic acidosis which may cause stomach pain, hyperventilation, shortness of breathe even though there may be improvement in your wheezing, cold feet and hands, irregular heartbeat or thirst.** [...]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	25 November 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	24 January 2018