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 octreotide, the scientific conclusions are as follows:

In view of the available data on atrioventricular block, from the literature and spontaneous reports, including in 4 cases a close temporal relationship, a positive dechallenge, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between octreotide and atrioventricular block, is at least a reasonable possibility, when octreotide is administered by i.v infusion at high doses. The PRAC concluded that the product information of products containing octreotide should be amended 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 octreotide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing *octreotide* 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 octreotide 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 4.4

A warning should be added as follows:

Cardiovascular related events

Atrioventricular blocks (including complete atrioventricular block) were reported in patients receiving high doses of continuous infusion (100 micrograms/hour) and in patients receiving bolus octreotide intravenously (50 micrograms bolus followed by 50 micrograms/hour continuous infusion). The maximum dose of 50 microgram/hour should therefore not be exceeded (see section 4.2). Patients who receive high doses of intravenous octreotide should be kept under appropriate cardiac monitoring.

- Section 4.9

Atrioventricular blocks (including complete atrioventricular block) were reported in patients receiving 100 micrograms/hour of continuous infusion and/or bolus octreotide intravenously (50 micrograms bolus followed by 50 micrograms/hour continuous infusion)

Package Leaflet

Section 2: Warnings and precautions

Octreotide may lower your heart rate and at very high doses may cause abnormal heart rhythm. Your doctor may monitor your heart rate during treatment.

Section 3: If you use more [product] than you should

~~No life-threatening reactions have been reported after overdose of [product].~~

The symptoms of overdose are: irregular heartbeat, low blood pressure, cardiac arrest, reduced supply of oxygen to the brain, severe upper stomach pain, yellow skin and eyes, nausea, loss of appetite, diarrhoea, weakness, tiredness, lack of energy, weight loss, abdominal swelling, discomfort, high level of lactic acid in the blood and **abnormal heart rhythm .**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 April 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 June 2021