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 carbetocin, the scientific conclusions are as follows:

A. In view of available data on 'bradycardia which could lead to cardiac arrest' from the literature, spontaneous reports including in 16 cases a close temporal relationship and in view of the structural similarity with oxytocin, the PRAC considers that a causal relationship between carbetocin and bradycardia leading to cardiac arrest is at least a reasonable possibility. The PRAC concluded that the product information of products containing carbetocin should be amended accordingly (i.e. the currently stated ADR "bradycardia" marked with the asterisk referring to oxytocin should be amended to state "bradycardia which can lead to cardiac arrest" and the asterisk should be deleted).

B. In view of available data on 'hypersensitivity (including anaphylactic reaction)' from spontaneous reports including 18 cases with a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between carbetocin and hypersensitivity (including anaphylactic reaction) is at least a reasonable possibility. The PRAC concluded that the product information of products containing carbetocin 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 carbetocin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing carbetocin 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 carbetocin 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 Not known:

Cardiac disorders

Not known: tachycardia, bradycardia ***which can lead to cardiac arrest*** *(currently stated asterisk, which refers to ADRs reported with oxytocin, should be deleted), arrhythmia*, myocardial ischaemia*, and QT prolongation**

** Reported with oxytocin (closely related in structure to carbetocin)*

The following adverse reaction(s) should be added under the SOC Immune system disorder with a frequency Not known:

Immune system disorders

Not known: hypersensitivity (including anaphylactic reaction)

Package Leaflet

Not known: frequency cannot be estimated from the available data

Fast heartbeat, ***Slow heartbeat which may lead to cardiac arrest (when the heart stops beating)***

Side effects seen with similar products that might be expected with carbetocin:

~~*Slow heartbeat*~~*, irregular heartbeat, chest pain, fainting or palpitations which may mean the heart is not beating properly.*

Allergic reactions (including sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating, low blood pressure and loss of consciousness)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	February CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	9 April 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	8 June 2023