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 iopamidol solution for injection the scientific conclusions are as follows:

In view of available data on acute generalized exanthematous pustulosis (AGEP) from spontaneous reports, including one case in which causality is certain, three cases in which causality is probable and one case in which causality is possible and in view of a plausible mechanism of action, the PRAC considers a causal relationship between iopamidol injection and acute generalized exanthematous pustulosis (AGEP) is at least a reasonable possibility.

In view of available data on hemiplegia and related disorders from spontaneous reports consisting of 74 cases of positive causality and specifically 7 cases of probable causality and 8 cases of possible causality reporting the PT hemiplegia and in view of a plausible mechanism of action, the PRAC considers a causal relationship between iopamidol injection and hemiplegia is at least a reasonable possibility.

In view of available data on Kounis syndrome from spontaneous reports including three cases in which causality is probable and two cases in which causality is possible and in view of a plausible mechanism of action the PRAC considers a causal relationship between iopamidol injection and Kounis syndrome is at least a reasonable possibility.

The PRAC concluded that the product information of products containing iopamidol solution for injection should be amended accordingly.

Update of section 4.4.and 4.8 of the SmPC to add a warning on SCARs and to add the adverse reaction “acute generalised exanthematous pustulosis” with a frequency of ‘not known’. The Package leaflet is updated accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction ‘hemiplegia’ with a frequency of ‘not known’. The Package leaflet is updated accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction ‘Kounis syndrome’ with a frequency of ‘not known’. 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 iopamidol solution for injection the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing iopamidol solution for injection is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products containing iopamidol solution for injection should be varied. To the extent that additional medicinal products containing iopamidol solution for injection 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)

The following changes to the product information of medicinal products containing the active substance iopamidol for injection are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), such Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (Lyell's syndrome or TEN) and acute generalised exanthematous pustulosis (AGEP), which can be life threatening, have been reported in patients administered <Product> (see section 4.8, undesirable effects). At the time of initiation, patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If signs and symptoms suggestive of these reactions appear, further use of <Product> should be withheld. If the patient has developed a severe cutaneous adverse reaction with the use of <Product>, <Product> must not be re-administered in this patient at any time.

- Section 4.8

The following text should be added under the 'Summary of safety profile'.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with <Product> administration (see section 4.4).

The following adverse reaction should be added under the SOC Skin and subcutaneous disorders with a frequency of 'not known':

Acute generalised exanthematous pustulosis (AGEP).

The following adverse reaction should be added for intravascular administration under the SOC Nervous system disorders with a frequency of 'not known':

Hemiplegia

The following adverse reaction should be added under the SOC Cardiac disorders with a frequency of 'not known':

Kounis syndrome

Package Leaflet

Section 2:

Tell your doctor before taking <Product>:

- **If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking <Product> or other iodinated contrast media.**

Take special care with <Product>:

Serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (Lyell's syndrome or TEN) and acute generalised exanthematous pustulosis (AGEP), have been reported in association with the use of <Product>.

Seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Section 4: Possible side-effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Tell your doctor straight away if you get any sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body). These are signs of an allergic reaction which can be serious and might require medical treatment.

Seek medical attention immediately if you notice any of the following symptoms:

- **reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).**
- **A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment (acute generalised exanthematous pustulosis).**

The frequency of these side-effects is not known.

Not known (cannot be estimated):
……
- **Inability to move one side of the body.**
- **heart attack caused by an allergic reaction**

…….

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	1 November 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	31 December 2020