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 iopromide, the scientific conclusions are as follows:

In view of available data on severe cutaneous adverse reactions (SCARs) from the literature and spontaneous reports, including in some cases a close temporal relationship and/or a positive re-challenge, and in view of a plausible class-effect and mechanism of action, the PRAC considers a causal relationship between iopromide and acute generalised exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) is at least a reasonable possibility. The PRAC concluded that the product information of products containing iopromide should be amended accordingly.

In view of available data on contrast induced encephalopathy from the literature and spontaneous reports, including in some cases a close temporal relationship, and in view of the class effect, the PRAC considers a causal relationship between iopromide and contrast induced encephalopathy is at least a reasonable possibility. The PRAC concluded that the product information of products containing iopromide 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 iopromide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing iopromide 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 iopromide 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:

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with unknown frequency in association with iopromide administration.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

In children, the initial presentation of a rash can be mistaken for an infection, and physicians should consider the possibility of a reaction to iopromide in children that develop signs of rash and fever.

Most of these reactions occurred within 8 weeks (AGEP 1-12 days, DRESS 2-8 weeks, SJS/TEN 5 days up to 8 weeks).

If the patient has developed a serious reaction such as SJS, TEN, AGEP or DRESS with the use of iopromide, iopromide must not be readministered in this patient at any time.

A warning should be amended as follows:

CNS disorders

Patients with CNS disorders may be at increased risk to have neurological complications in relationship to iopromide administration. Neurological complications are more frequent in cerebral angiography and related procedures.

Encephalopathy has been reported with the use of iopromide (see section 4.8). Contrast encephalopathy may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema. Symptoms usually occur within minutes to hours after administration of iopromide and generally resolve within days.

Factors which increase blood-brain barrier permeability facilitate the passage of the contrast medium into cerebral tissue, possibly leading to CNS reactions**, for instance encephalopathy**.

If contrast encephalopathy is suspected, appropriate medical management should be initiated and administration of iopromide must not be repeated.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency of unknown:

- **Acute generalised exanthematous pustulosis**

- **Drug reaction with eosinophilia and systemic symptoms**

The following adverse reaction(s) should be added under the SOC Nervous system disorders with a frequency of unknown:

- **Contrast encephalopathy**

Package Leaflet

• Section 2

Warnings and precautions

Talk to your doctor or nurse before taking X:

- **If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after use of X.**

Take special care with <medicine>:

Serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with <medicine> use. Seek medical attention immediately if you notice any of the signs described in section 4.

Nervous system disturbances

During or shortly after the imaging procedure you may experience a short-term brain disorder called encephalopathy. Tell your doctor straight away if you notice any of the signs and symptoms related to this condition described in section 4.

• Section 4

Seek medical attention immediately if you notice any of the following signs and symptoms (whose frequency is not known):

- **Reddish patches on the trunk, the patches are target-like macules or circular, 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).**
- **Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).**
- **A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever after the imaging procedure (acute generalised exanthematous pustulosis).**
- **Short term brain disorder (encephalopathy) which can cause memory loss, confusion, hallucinations, difficulties with vision, loss of vision, seizures, loss of coordination, loss of movement in one side of the body, problems with speech, 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 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 April 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 June 2021