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 iohexol the scientific conclusions are as follows:

In view of available data on beta-adrenergic blocking agents from the literature, the PRAC considers a causal relationship between iohexol, beta-adrenergic blocking agents and an increased risk of bronchospasm in asthmatic patients, as well as reduced effect of adrenaline treatment, established. The PRAC concluded that the product information of products containing iohexol should be amended accordingly.

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

Warnings should be amended as follows:

Hypersensitivity

Patients using beta-adrenergic blocking agents, particularly asthmatic patients, may have a lower threshold for bronchospasm and are less responsive to treatment with beta agonists and adrenaline, which may necessitate the use of higher doses. These ~~P~~**p**atients ~~using β-blockers~~ may **also** present with atypical symptoms of anaphylaxis which may be misinterpreted as vagal reaction.

…

CNS disturbances

Encephalopathy has been reported with the use of iohexol (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 iohexol, and generally resolve within days.
Factors which increase blood-brain barrier permeability will ease the transfer of contrast media to brain tissue and may lead to possible CNS reactions for instance encephalopathy.
Caution is advised in intravascular application to patients with acute cerebral infarction or acute intracranial bleeding as well as in patients with diseases causing disturbance of the blood-brain barrier, **and** in patients with cerebral oedema, acute demyelinisation or advanced cerebral atherosclerosis.
If contrast encephalopathy is suspected, appropriate medical management should be initiated and iohexol must not be readministered.

Package Leaflet

- Section 2

Warnings and precautions

Talk to your doctor before taking X

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.

Other medicines and <drug name>

…

Tell your doctor if:

Beta-blockers may increase your risk of experiencing breathing difficulties and may interfere with the treatment of severe allergic reactions, which is a risk of <product name>.

- Section 4

…

Not known: frequency cannot be estimated from the available data

- Short term brain disorders (encephalopathy) **which can cause 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