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 iobitridol scientific conclusions are as follows:

Following the assessment of the reported cases of DRESS it is considered that there is sufficient evidence to warrant an update to section 4.3, 4.4 and 4.8 of the Summary of Product Characteristics with a corresponding update to section 2 and 4 of the Package Leaflet. Evidence to substantiate this is provided by post-marketing data with a total of six supportive cases. All cases are serious but none reported a fatal outcome. Causality is probable in one case, possible in one case and cannot be definitely excluded in the remaining four cases. As Acute Generalised Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and Lyell's syndrome or Toxic Epidermal Necrolysis are already listed in section 4.8, the update to 4.4 also includes reference to these SCARs, with corresponding updates to the package leaflet as required.

Biological plausibility exists as iodinated contrast media are known to cause immediate and delayed allergic reactions largely related to their osmolarity and/or ionic charge.

Other severe cutaneous adverse reactions are a well-known risk of iodinated contrast media agents with SJS, Lyell's syndrome or TEN and AGEP already listed for iobitridol in the context of delayed hypersensitivity reactions and DRESS is included in section 4.4 and 4.8 of another iodinated contrast agent, Optiray (ioversol).

On the basis of the cumulative review of bradycardia performed in this PSUR it is recommended that the product information is updated to include bradycardia. Evidence to substantiate this is provided by post-marketing data with a total of 17 reported cases. All cases are serious cases and in sixteen cases iobitridol is the only suspect drug. Causality is probable in four cases and possible in the remaining thirteen cases. Pathophysiological mechanisms for bradycardia in association with contrast agents have been described including hypersensitivity, vasovagal reactions or acetylcholinesterase inhibition and bradycardia is listed for a number of other iodinated contrast agents across the class.

Following assessment of the data on bradycardia, including the reported cases, it is considered that there is sufficient evidence to warrant an update to section 4.8 of the Summary of Product Characteristics with a corresponding update to section 4 of the package leaflet.

In addition, similar to other agents in the class, tachycardia is a known ADR of Xenetix and has previously been listed in section 4.8 of the SmPC. To ensure the safety information in the PL is aligned with the SmPC in relation to bradycardia (and tachycardia) it is recommended that the PL is updated to include both increased or decreased heart rate in Section 4.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for iobitridol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing iobitridol 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 iobitridol 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 iobitridol are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

Section 4.3

History of major immediate or delayed skin reaction (see section**s 4.4** and 4.8) to **i**obitridol injection;

Section 4.4

4.4.2 Precautions for use

4.4.2.1 Intolerance to iodinated contrast agents:

Prior to the examination:

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• The patient must be informed of the possibility of delayed reactions (for up to 7 days) (see section 4.8, Undesirable effects).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) such as drug reaction/rash with eosinophilia and systemic symptoms (DRESS), 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 iobitridol (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. Iobitridol should be discontinued immediately upon suspicion of a severe hypersensitivity reaction. If the patient has developed a severe cutaneous adverse reaction with the use of iobitridol, iobitridol must not be re-administered in this patient at any time (see section 4.3).

Section 4.8

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

Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

The following adverse reaction should be added under the SOC 'cardiovascular disorders' with a frequency of 'rare':

Bradycardia

Package Leaflet

Section 2:

Do not use Xenetix:

- **If you have previously developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Xenetix.**

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Warnings and Precautions

Before the examination, you should inform your doctor if you are in any of the following situations:

-you have previously reacted to an iodinated contrast agent during an examination

-you have previously developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Xenetix or other iodinated contrast media.

……

-You have any other disease.

Take special care with Xenetix:

Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (Lyell's syndrome or TEN) and acute exanthematous pustulosis (AGEP), which can be life-threatening, have been reported with the use of Xenetix.

If you develop a serious rash or another of these skin symptoms, contact your doctor or seek medical attention immediately.

Section 4: Possible side-effects

'There is a small risk (rare) that you may have an allergic reaction to Xenetix. Such reactions can be severe and may exceptionally result in shock (very rare case of allergic reaction that could put your life in danger). An allergy can be recognised by the following effects:

• reactions that appear very rapidly (often within an hour) with pimples on the skin, redness (erythema) and itching (localised or extensive hives), sudden swelling of the face and neck (angioneurotic oedema)

• reactions that appear later on the skin, i.e. red pimples (macular or papular eruptions) and in exceptional cases, serious extensive skin lesions with the appearance of blisters on the body (Lyell's or Stevens-Johnson syndrome), **red, scaly widespread rash with bumps under the skin and blisters accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis) or widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (drug reaction with eosinophilia and systemic symptoms which is also known as DRESS or drug hypersensitivity syndrome). See also section 2.**

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Other possible side effects:

- Effects on the heart and blood vessels**, including increased or decreased heart rate'**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	15 March 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	14 May 2020