COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Iopamidol ADOH 408 mg/ml (200 mg iodine/ml), solution for injection (iopamidol)

NL License RVG: 128669

Date: 15 November 2022

This module reflects the scientific discussion for the approval of Iopamidol ADOH 408 mg/ml (200 mg iodine/ml), solution for injection. The marketing authorisation was granted on 18 May 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Iopamidol ADOH 408 mg/ml (200 mg iodine/ml), solution for injection from ADOH B.V.

The product is indicated for imaging of the lumbar, thoracic and cervical spine (radiculography and myelography) and for intrathecal injection in CT myelography.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the European Reference Product (ERP) Solutrast M 200 mg/ml, solution for injection. This product has been registered in Germany by marketing authorisation holder (MAH) Bracco Imaging Deutschland GmbH (German MA number 2158.00.00).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Iopamidol ADOH 408 mg/ml (200 mg iodine/ml), solution for injection is a clear and colourless solution.

The product is packed in a type I glass vial closed with a bromobutyl rubber stopper covered with an aluminium-plastic cap. Each vial of 10 ml solution contains as active substance 4080 mg of iopamidol, as 2000 mg of iodine. One ml solution for injection contains 408 mg iopamidol, as 200 mg iodine.

The excipients are trometamol, sodium calcium edetate, sodium hydroxide, hydrochloric acid and water for injection.

II.2 Drug Substance

The active substance is iopamidol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Iopamidol is a white or almost white powder that is freely soluble in water, very slightly soluble in methanol and practically insoluble in ethanol and methylene chloride. There are no reports of polymorphic nature of commercially produced iopamidol. Since the active substance is administered parenterally as an aqueous solution, the polymorphic properties will have no impact on pharmacokinetic properties.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. During development the European reference product was not available on the market. Therefore, the USA equivalent was used for the development of the drug product. This was deemed acceptable. Prior to the development of formulation, critical formulation variables of bulk solution and finished product were identified by assessing CQAs (critical quality attributes), the manufacturing process and dosage form characteristics and by referencing prior knowledge. The risk evaluation of the of critical formulation variables against the drug product CQAs is considered acceptable. Extensive information and test data have been provided for the proposed glass vial and rubber stopper.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Extensive information and test data have been provided for the proposed glass vial and rubber stopper. The proposed acceptance criteria for the critical proposed parameters and in-process control tests are considered acceptable. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
All excipients meet the requirements of the Ph.Eur. monographs. The additional microbial requirements for calcium edetate and trometamol are considered acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH, clarity of solution, free iodine, iodide, free aromatic amines, extractable volume, particle contamination, related substances, sterility, bacterial endotoxins and assay. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The elemental impurities risk evaluation and nitrosamine risk evaluation meet the requirements by the ICH and EMA respectively. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the product. Based on a photostability study, it was concluded that the drug product should be protected from light. On basis of the data submitted, a shelf life was granted of 2 years, without special temperature storage conditions. The labelled storage conditions are to store in the original package in order to protect from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Iopamidol ADOH has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Iopamidol ADOH is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Solarist M which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Iopamidol is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Iopamidol ADOH 200 mg/ml solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The excipients and quantitative composition of Iopamidol ADOH is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Iopamidol ADOH 200 mg/ml solution for injection.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	-
Important potential risks	-
Missing information	Use in pregnancy

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the reference product Solutrast. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Dutch. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Iopamidol ADOH 408 mg/ml (200 mg iodine/ml), solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Solutrast M 200 mg/ml, solution for injection. Solutrast is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Iopamidol ADOH 408 mg/ml (200 mg iodine/ml), solution for injection with the reference product, and have therefore granted a marketing authorisation. The procedure was finalised with a positive outcome on 18 May 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	N/A	N/A	N/A	N/A