LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Dotavision
(gadoteric acid, gadolinium oxide, tetraxetan)

SE/H/2314/01/DC

This module reflects the scientific discussion for the approval of Dotavision. The procedure was finalised on 2024-11-27. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Dotavision, 0,5 mmol/ml, Solution for injection.

The active substance is gadoteric acid, gadolinium oxide, tetraxetan. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Dotavision, 0,5 mmol/ml, Solution for injection, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FR as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Dotarem, 279,3 mg/ml, solution for injection authorised in Sweden since 1995, with Guerbet as marketing authorisation holder.

Potential similarity with orphan medicinal products

N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of gadoteric acid are well known. As gadoteric acid is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Dotavision is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Dotavision 0.5 mmol/ml solution for injection from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence study has been submitted. The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the currently authorised product. The applied product also contains the same excipients in similar amounts as the reference product. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Since this is a generic where no bioequivalence study is needed (see pharmacokinetics above), additional data is not necessary.
A clinical overview has been submitted where relevant literature data are summarised to support the application.

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 Dotavision.

Part II Safety specification

Summary of safety concerns	
Important identified risks	• Nephrogenic systemic fibrosis (NSF)
Important potential risks	• Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues • Adverse clinical effects of accumulation and retention of gadolinium in the brain
Missing information	• Clinical significance of gadolinium accumulation in organs and tissues other than brain tissues • Clinical significance of gadolinium retention in the brain • Safety in pregnancy and lactation

The summary of safety concerns is identical to the reference product.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Additional pharmacovigilance activities related to the safety concerns NSF, gadolinium accumulation in organs and tissues other than brain tissues, gadolinium accumulation in bone and accumulation and retention of gadolinium in the brain have been implemented or have been finalized by the MAH of the reference product.
EXDRA GmbH will regard the studies and closely follow up on any result of these studies. EXDRA GmbH will implement any new safety actions in alignment with the reference product for the future.

Part V Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Additional risk minimisation measures have already been implemented for the important potential risk and missing information concerning accumulation or retention of gadolinium in the brain or other organs/tissues. As a result of the Referral procedure EMEA/H/A-31/1437 (closed in November 2017) a joint Direct Healthcare Professional Communication (DHPC) was published and disseminated in the European countries in 2018. The DHPC was sent out by all MAHs in order to inform HCPs about the potential risk of gadolinium accumulation and retention in the brain with the advice to use gadolinium contrast agents only when essential diagnostic information cannot be obtained with unenhanced scans and to always use the lowest dose that provides sufficient enhancement for diagnosis. This is reflected in the proposed wording of SmPC and PL.
Therefore, there are not any current additional risk minimisation measures for Dotavision.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 27 Nov 2023 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to *Cyclolux 0.5 mmol/ml solution for injection in vials package* DE/H/4015/01/01-02/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Dotavision, is found adequate. There are no objections to approval of Dotavision, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Dotavision, 0,5 mmol/ml, Solution for injection was positively finalised on 2024-11-27.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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