Bundesinstitut
für Arzneimittel
und Medizinprodukte

PUBLIC ASSESSMENT REPORT

Decentralised Procedure

Dotagraf 0,5 mmol/ml Injektionslösung
Procedure Number: DE/H/3944/01-02/DC

Cyclolux 0,5 mmol/ml Injektionslösung
Procedure Number: DE/H/4015/01/01-02DC

Active Substance:
Gadoteric acid

Dosage Form:
Solution for injection

Marketing Authorisation Holder in the RMS, Germany:
Jenapharm GmbH & Co. KG (DE/H/3944/01-02/DC)
SANOCHEMIA Pharmazeutika AG (DE/H/4015/01/01-02DC)

Publication:
18.09.2019

This module reflects the scientific discussion for the approval of Dotagraf / Cyclolux 0,5 mmol/ml Injektionslösung. The procedures were finalised on 03.06.2014.

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Dotagraf 0,5 mmol/ml Injektionslösung (DE/H/3944/01-02/DC) Cyclolux 0,5 mmol/ml Injektionslösung (DE/H/4015/01-02/DC)
INN (or common name) of the active substance(s):	Gadoteric acid
Pharmaco-therapeutic group (ATC Code):	V08CA02
Pharmaceutical form(s) and strength(s):	Solution for injection
Reference Number(s) for the Decentralised Procedure	DE/H/3944/01-02/DC DE/H/4015/01-02/DC
Reference Member State:	DE
Member States concerned:	AT; BE; ES; FR; IT (DE/H/3944/01-02/DC) AT; CZ; EL; ES; HU; PL; SK; UK (DE/H/4015/01-02/DC)
Marketing Authorisation Holder (name and address)	*DE/H/3944/01-02/DC* Jenapharm GmbH & Co. KG Otto-Schott-Str. 15 07745 Jena Germany *DE/H/4015/01-02/DC* SANOCHEMIA Pharmazeutika AG Boltzmanngasse 11 1090 WIEN Austria
Names and addresses of manufacturer(s) responsible for batch release in the EEA	Sanochemia Pharmazeutika AG (BS 1) Landeggerstr. 7 2491 Neufeld an der Leitha Austria

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for Dotagraf 0,5 mmol/ml Injektionslösung and Cyclolux 0,5 mmol/ml Injektionslösung, in the diagnostic use of

Intensification of the contrast in Magnetic Resonance Imaging (MRI) Techniques for a better visualization/delineation:

- MRI of the CNS including lesions of the brain, spine, and surrounding tissues
- Whole body MRI including lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system.
- MR angiography including lesions or stenoses of the non-coronary arteries,

is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

This decentralised application concerns a generic version of Gadoteric acid, under 2 trade names: Dotagraf 0,5 mmol/ml Injektionslösung (DE/H/3944/001-002/DC) and Cyclolux 0,5 mmol/ml Injektionslösung (DE/H/4015/01-02/DC). In this Assessment Report, the name Gadoteric acid is used.

The originator product is Dotarem 0.5 mmol/ml solution for injection by Guerbet Nederland BV, registered since 1991-04-16.

With DE as the Reference Member State in this Decentralized Procedure Jenapharm GmbH & Co. KG and Sanochemia Pharmazeutika AG applied for the Marketing Authorisations for Gadoteric acid in AT, BE, CZ, EL, ES, FR, HU, IT, PL, SK, and UK.

Gadoteric acid is a paramagnetic diagnostic contrast agent for MRI used for visualization / delineation of lesions of the brain, spine, and surrounding tissues; whole body MRI including lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast and musculoskeletal system; and of lesions or stenosis of the non-coronary arteries (MR Angiography).

Gadoteric acid is a macrocyclic chelate and has been classified as an agent that carries a low risk for nephrogenic systemic fibrosis (NSF).

In neurological examinations, the dose can vary from 0.1 to 0.3 mmol/kg body weight (BW), corresponding to 0.2 to 0.6 ml/kg BW. After administration of 0.1 mmol/kg BW to patients with brain tumours the additional dose of 0.2 mmol/kg BW may improve tumour characterisation and facilitate therapeutic decision making. The recommended dose for whole body MRI and MRI of other organs is 0.1 mmol/kg (i.e. 0.2 ml/kg BW) intravenous (i.v.) injection to provide diagnostically adequate contrast. If in angiography satisfactory images of an extensive vascular territory administration are not gained a second consecutive injection of 0.1 mmol/kg BW, equivalent to 0.2 ml/kg BW is justified. However, if the use of 2 consecutive doses of Gadoteric acid is anticipated prior to commencing angiography, use of 0.05 mmol/kg BW equivalent to 0.1ml/kg BW for each dose may be of benefit, depending on the imaging equipment available.

II.2 About the product

Gadoteric acid is a paramagnetic contrast agent for magnetic resonance imaging (MRI). The contrast-enhancing effect is mediated by gadoteric acid which is a ionic gadolinium complex composed out of Gadolinium oxide and 1,4,7,10 tetraazacyclododedane- N,N',N'',N''' tetraacetic acid (Dota), and present as meglumine salt. When a suitable scanning sequence (e.g. T1-weighted spin-echo technique)

is used in proton magnetic resonance imaging, the gadolinium ion-induced shortening of the spin-lattice relaxation time of excited atomic nuclei leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues.

II.3 General comments on the submitted dossier

The active substance is not considered a new active substance.

The submitted dossier is of acceptable quality.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GCP

Due to their rather old publication date some of the studies referred to in the Clinical Overview were not performed according to good clinical practice (GCP). However, the quality of the clinical trials corresponds to those of other drugs evaluated in the same time period. Additional studies conducted according to GCP would not provide further information and are not planned by the applicant.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Introduction
The chemical-pharmaceutical documentation and Expert Report in relation to the medicinal products are of sufficient quality in view of the present European regulatory requirements.

Drug substance
The drug substance gadoteric acid (as a meglumine salt) is not isolated but formed in-situ during the manufacturing process of the drug product.
Gadoteric acid consists of the two components gadolinium oxide and the chelating agent DOTA. For DOTA an ASMF has been provided. Both components have been adequately described.
The proposed retest periods are supported.

Drug Product
The drug products are solutions for injection containing a strong complex of gadolinium (III) and teric acid (DOTA) with strength of 0.5 mmol (gadolinium)/ml. The acidic complex is neutralized with the excipient meglumine to the appropriate pH.
The development of the product has been described, the choice of excipients is justified and their functions explained.

The drug products are intended for single use and multiple use.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented.
Batch analysis has been performed on three batches. The batch analysis results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
The proposed shelf-life of 36 months – with no special storing conditions – is supported.

III.2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of gadoteric acid are well known. Gadoteric Acid is a widely used, well-known active substance; the applicant has not provided additional studies and further studies are not required. The overview based on literature review is thus appropriate.

The non-clinical overview is dated July 2013. The report refers publications up to year 2013.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The non-clinical sections of the SmPC/ PIL are adequate. There are no remaining issues.

There are no objections to approval of Dotagraf 0,5 mmol/ml Injektionslösung and Cyclolux 0,5 mmol/ml Injektionslösung from a non-clinical point of view.

Environmental Risk Assessment (ERA)
Dotagraf 0,5 mmol/ml Injektionslösung and Cyclolux 0,5 mmol/ml Injektionslösung are 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.3 Clinical aspects

The clinical overview is dated 09 August 2013. The Overview refers publications up to year 2013. The clinical overview on the clinical pharmacology, efficacy, and safety is adequate.

Pharmacokinetics
Pharmacokinetic properties of gadoteric acid are well known. As gadoteric acid is a widely used, well-known active substance, no further pharmacokinetic studies are required and the applicant provides none.

After i.v. administration gadoteric acid is quickly distributed in the extracellular fluids. The distribution volume is approximately 18 l almost equal to the volume of extracellular fluid. Gadoteric acid does not bind to proteins like serum albumin. Gadoteric acid is eliminated rapidly (89% after 6 h, 95% after 24 h) in unchanged form through the kidneys by glomerular filtration. Excretion via the faeces is negligible. No metabolites were detected. The elimination half-life amounts to about 1.6 h in patients with a normal renal function. In renally impaired patients, the elimination half-life was increased to approximately 5 h for a creatinine clearance between 30 and 60 ml/min and approximately 14 h for a creatinine clearance between 10 and 30 ml/min. In animal experiments it has been demonstrated that gadoteric acid can be removed by dialysis.

Pharmacodynamics
Pharmacodynamic properties of gadoteric acid are well known. As gadoteric acid is a widely used, well-known active substance, no further Pharmacodynamic studies are required and the applicant provides none.

Gadoteric acid is a paramagnetic contrast agent for magnetic resonance imaging (MRI). When a suitable scanning sequence (e.g. T1-weighted spin-echo technique) is used in proton magnetic resonance imaging, the gadolinium ion-induced shortening of the spin-lattice relaxation time of excited atomic nuclei leads to an increase of the signal intensity and, hence, to an increase of the image contrast of certain tissues.

Clinical efficacy
This marketing authorization concerns a bibliographical application. No clinical or pre-clinical studies have been performed with the product under consideration. This is reasonable and justified, since gadoteric acid is generally established for medicinal use and is acknowledged as being both efficient and possessing an acceptable level of safety.

The efficacy of gadoteric acid has been demonstrated in numerous clinical studies and a selection of those of highest priority has been made. In particular technical performance has been exhaustively described in the literature made available.

Clinical safety
There is extensive post marketing data for gadoteric acid available.

Side effects in association with the use of gadoteric acid are usually mild to moderate in intensity and transient in nature. A sensation of heat, cold, or pain at the injection site is the most frequently observed reaction. The incidence of adverse reactions following administration of gadoterice acid in the majority of published studies to date is less than 1%. Anaphylactoid reactions induced by gadolinium-containing products are rare, but there are a few published case reports of anaphylactic shock following administration of gadoteric acid. The risk of hypersensitivity is independent of the dose injected.

Although macrocyclic chelates including gadoteric acid have been categorised as having a low risk of NSF, restrictions and warnings as proposed for the product information (PI) of gadolinium-containing contrast agents apply also for gadoteric acid. Prior to administration of gadoteric acid, patients should be screened for renal dysfunction by obtaining laboratory tests. Testing for renal dysfunction is especially important in patients aged 65 years and older. The risk of NSF and related precautions are adequately addressed in the proposed PI.

Gadoteric acid is included in the PSUR worksharing procedure and a Final PSUR assessment report and respective CSP was finalised in July 2012 (NL/H/PSUR/0007/002).

Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The following safety concerns have been identified by the applicant:

Summary of safety concerns	
Important identified risks	• Nephrogenic Systemic Fibrosis (NSF) • Hypersensitivity
Important potential risks	• Convulsions • Teratogenicity
Missing information	• Gadolinium accumulation in bone, including long term effects

The following additional risk minimisation measures are proposed:

Education of prescribers	Education of prescribers and physicians who manage renally impaired patients: To inform and educate the prescribers i.e. physicians to: • Use Gd-enhanced MRI only after careful evaluation of the need for severely renally impaired patients. • Use of the smallest amount of gadolinium as necessary for a reliable diagnosis. • Be informed how to suspect and confirm a diagnosis of NSF. • Be informed how to report any NSF case to the local Health Authorities, and/or Sanochemia if Gadoteric acid Sanochemia is used. Objective and justification of why needed: Commission Decision Referral procedure EMEA/H/A-31-1097; to inform healthcare professionals on SPC update and risk of NSF. Dear Healthcare Professional Communication: National Competent Authorities should ensure that prescribers will be informed of the measures agreed by CHMP to minimise the risk of NSF. The communication should be based on the "key message document" agreed by CHMP.
	This information was already communicated by the competent authorities to the health care professionals.
Product identification to enable reliable identification of GdCA: to enable reliable identification of GdCA to compare the risk between various GBCA products.	<u>Detachable ("sticky") labels on the vials and syringes of the Gd-containing products:</u> In order to have a harmonised traceability method across Europe for the effective monitoring of the use of Gd-containing contrast agents the National Competent Authorities, coordinated by the Reference Member State (where applicable) should ensure the implementation by the MAHs of detachable ("sticky") labels on the vials and syringes of the Gd-containing contrast agents. "Sticky" labels will be implemented for Gadoteric acid in all countries.

The amended RMP version 1.2 is considered appropriate.

Periodic Safety Update Report (PSUR)
In accordance with the revised legislation on pharmacovigilance (Directive 2010/84/EU) the list of European Union Reference Dates (the EURD list) of PSURs has been established and published by EMA. Marketing authorisation holders shall continuously check the EMA web-portal for the DLP and frequency of submission of the next PSUR.

Common renewal date
Common renewal date is 03.06.2020.

Legal status
The medicinal product is subject to medical prescription.

User Test
The readability test was performed in English in London, England. It consisted of sufficient questions on the content of the PL including open questions and a rating scale question regarding the layout/design of the PL.

The volunteer population for this study round consisted of male and female test subjects. The population tested was acceptable as it was balanced for gender age and level of education. The evaluation of the responses was acceptable.

Overall the results of the study were very well (100% correct answers to the questions) and the predefined success criteria were fulfilled.

The results demonstrate a high level of comprehension of product related information.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data. Approval is recommended from the clinical point of view.

The application is approved. For intermediate amendments see current product information.