

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Gadoteerzuur Guerbet 0.5 mmol/ml solution for injection in vials
Gadoteerzuur Guerbet 0.5 mmol/ml,
solution for injection in vials for multiple use
Gadoteerzuur Guerbet 0.5 mmol/ml,
solution for injection in pre-filled syringes
Guerbet, France

gadoteric acid**

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/2028/001-003/DC
Registration number in the Netherlands: RVG 107972-107974**

9 November 2011

Pharmacotherapeutic group:	paramagnetic contrast media
ATC code:	V08CA02
Route of administration:	parenteral
Therapeutic indication:	Intensification of the contrast in Magnetic Resonance Imaging for a better visualization/delineation: <ul style="list-style-type: none"> - of lesions of the brain, spine, and surrounding tissues; - of lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system. - of lesions or stenoses of the non-coronary arteries (MR Angiography).
Prescription status:	prescription only
Date of authorisation in NL:	31 August 2011
Concerned Member States:	Decentralised with BE, DE, and FR
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Gadoteerzuur Guerbet 0.5 mmol/ml, solution for injection in vials/vials for multiple use/pre-filled syringes, from Guerbet. The date of authorisation was on 31 August 2011 in the Netherlands.

The product is indicated for Intensification of the contrast in Magnetic Resonance Imaging (MRI) for a better visualization/delineation:

- of lesions of the brain, spine, and surrounding tissues
- of lesions of the liver, kidneys, pancreas, pelvis, lungs, heart, breast, and musculoskeletal system.
- of lesions or stenoses of the non-coronary arteries (MR Angiography).

This medicinal product is for diagnostic use only.

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

Gadoteric acid Guerbet is a paramagnetic contrast agent for magnetic resonance imaging. 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 tetraazacyclododecane- N,N',N'',N''' tetraacetic acid (Dota), and present as meglumine salt.

The paramagnetic effect (relaxivity) is determined from the effect on spin-lattice relaxation time (T1) about $3.4 \text{ mmol}^{-1} \cdot \text{L} \cdot \text{sec}^{-1}$ and on the spin-spin relaxation time (T2) about $4.27 \text{ mmol}^{-1} \cdot \text{L} \cdot \text{sec}^{-1}$.

Gadoteric acid does not pass the intact blood-brain barrier and therefore does not accumulate in healthy brain tissue or in lesions featuring an intact blood-brain barrier.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Dotarem 0.5 mmol/ml, solution for injection. This product was registered in France in 1989 and in the Netherlands in 1991 (NL licence RVG 14203) and Germany via a Mutual Recognition Procedure with the Netherlands acting as the RMS (NL/H/0381/MR). Guerbet is also the MA holder of Dotarem. Guerbet states that the qualitative and quantitative composition and the manufacturers of the proposed generic product are strictly identical to those of Dotarem. In addition, reference is made to Dotarem authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Gadoteerzuur Guerbet 0.5 mmol/ml in vials/vials for multiple use/pre-filled syringes are products for parenteral use in an aqueous solution, they are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

General information

In the manufacturing of the drug product by mixing the components DOTA and Gadolinium oxide the complex gadoteric acid is formed.

DOTA

DOTA is a white powder which is soluble in water and practically insoluble in dimethylformamide, hexane, ethanol and methanol.

Manufacture

There are two manufacturers for the chelating agent DOTA and one manufacturer for gadolinium oxide (which form the complex Gd-DOTA or gadoteric acid). For all these manufacturers full information is present in the dossier. In-process controls are not applicable. Adequate specifications for three starting materials are applied. Adequate specifications on the intermediate are applied.

Quality control of drug substance

For DOTA adequate specifications on identification, assay (by potentiometric titration), HPLC related substances, HPLC purity of DOTA, microbial purity, residual ethanol, KF water content and some other parameters are applied. All analytical methods have been adequately described and validated. Batch analysis results for 3 industrial batches of DOTA are provided. All results met the set requirements.

Stability of drug substance

Three industrial batches of each of the two manufacturing processes - all manufactured by one specific manufacturer -, have been put on stability at 25°C/60% RH for 3 years and at 40°C/75% RH for 6 months. Results for all parameters remain constant. Based on the data provided, a retest period of 3 years was accepted.

Gadolinium oxide

Gadolinium oxide is a white fine powder, insoluble in water and soluble in nitric / hydrochloric acids. The product is hygroscopic and absorbs carbon dioxide from the air.

Manufacture

The manufacturing process has been adequately described, and the batch size ranges were provided. An adequate specification is applied for starting material gadolinium nitrate.

Quality control of drug substance

An adequate specification is applied for gadolinium oxide: a set of routine controls applied by the MAH and drug product manufacturer with tests on appearance and odour, identification, loss on ignition, loss on drying, microbial contamination and assay by AAS, and a full set of controls applied by supplier, with additional tests on eight foreign oxides and on fourteen rare earth elements. All methods have been described; most methods are the same as used for testing gadolinium nitrate. The assay method for gadolinium oxide by AAS, the test for microbial contamination, and the tests on foreign and rare earth oxides are adequately validated. Batch analysis results for the routine control tests have been provided for 3 industrial batches. Assay results for gadolinium oxide are 99.1-99.6%. Full batch analyses including results on foreign and rare earth oxides are provided for 10 industrial batches.

Stability of drug substance

Gadolinium oxide is known in the literature to be a very stable inorganic compound as shown below:

- Gd₂O₃ content: the oxidation state of Gd in Gadolinium oxide is +III. Gadolinium oxide has only two oxidation states (0 and +III) also it cannot be more oxidized.
- Temperature: the calcinations in the final step of the manufacturing process have to be performed at least at 850°C. Thereafter, Gadolinium oxide is not subjected to heat degradation. Moreover, Gadolinium oxide is thermodynamically very stable with an enthalpy of formation equal to – 430 Kcal/mol at 298°K.
- Melting point: the melting point is 2340°C.
- Hygroscopy: the manufacturer's stability studies have shown that the maximal absorption of water is 0.2%.

Three batches have been put on stability by one supplier at ambient conditions, and three batches by Guerbet also at ambient conditions. Based on the long term stability results the active substance component Gadolinium oxide can be considered to be stable for three years. A re-test period of 3 years can be granted for Gadolinium oxide packed in the proposed packaging.

Medicinal Product

Composition

The composition of the proposed product Gadoteric acid 0.5 mmol/ ml, solution for injection is an aqueous injectable solution of Gadoteric acid. Gadoteric acid is solubilised by meglumine. Gadoteric acid is present in the proposed product as the meglumine salt. As DOTA complexes Gadolinium to give Gadoteric acid, the reaction is as follows:

$2 \text{Dota} + \text{Gd}_2\text{O}_3 \rightarrow 2 \text{Dota-Gd} + 3 \text{H}_2\text{O}$ which means that per 100 ml 0.05 gmol DOTA is present or 0.5 mmol/ml.

The excipients are meglumine and water for injections. The pH of the drug product is between 6.5 – 8.0 and the osmolality is 1350 mOsm/kg.

The vial product is packaged in type II clear glass vials (5-10-15-20-60-100 ml), closed with an elastomeric type I chlorobutyl rubber stopper and crimped with an aluminum cap.

The syringe product is packaged in type I clear glass syringes (10-15-20 ml) coated silicone oil, fitted with a type I synthetic polyisoprene/bromobutyl, latex free tip cap and a type I chlorobutyl, latex free plunger stopper coated with silicone oil.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. DOTA forms a complex of the Gadolinium ion to give gadoteric acid. The complex of the Gadolinium ion reduces the toxicity of the free ion injected intravenously without affecting its paramagnetic properties. Gadoteric acid in aqueous solution has a free carboxyl group, which gives it an acidic pH. Neutralization of this group with meglumine allows the pH to be adjusted to a value to physiological pH. The Gd-DOTA concentration of the gadoteric acid solution (0.5 mol/L) takes into account physico-chemical (solubility), physiological (osmolality) and clinical (effective dose and volume injected) constraints. Refined studies have been performed studying effect of pH, effects of (slight) excess of DOTA, and resulting free gadolinium levels. All development know-how is based on long-term experience with the Dotarem product. All development sections are considered to be of adequate quality.

Container closure systems

Gadoteric acid is packaged in type II clear glass vials, closed with an elastomeric type I chlorobutyl rubber stopper and crimped with an aluminium cap. The type II glass vials comply with the Ph. Eur.* monograph 3.2.1 "*Glass containers for pharmaceutical use*". The rubber stopper type I complies with the Ph. Eur. 3.2.9 "*Rubber for closures for containers for aqueous parenteral preparations*".

The syringes BD Hypak™ have a capacity of 10 or 20 ml. The syringes consists of:

- A *syringe barrel* made of type I glass according to the Ph. Eur.-monograph 3.2.1 "*Glass containers for pharmaceutical use*", siliconized with a 1000 cSt viscosity silicone oil.
- A *plunger stopper* and a *tip-cap* made of a chlorobutyl-isoprene and polyisoprene-bromobutyl elastomer respectively. The rubber complies with Ph. Eur. 3.2.9. The plunger stopper is siliconized with a 1000 cSt.

The specifications laid down for the stopper and plunger materials are acceptable.

Compatibility studies

The results of the compatibility tests for gadoteric acid solutions in vials and syringes are acceptable; this also means that the tip caps consisting of polyisoprene-bromobutyl rubber are acceptable and that the tip cap and plunger stopper are suitable for application in syringes of gadoteric acid solutions.

Manufacturing process

The most representative industrial batch size is 400 L but multiples or submultiples of 200 L, from 200 L up to 600 L can be manufactured, according to the needs of drug product. A batch formula – in accordance with the drug product composition – is provided for a 200 L quantity. The manufacturing process of gadoteric acid bulk solution is the same for the manufacturing of both vials and syringes.

The manufacturing requires a conventional process and all operations are carried out using stainless steel equipment, all in air controlled atmosphere and in accordance with GMP rules. The clarity of solution and the content of free Gadolinium are checked by IPCs.

Validation studies:

Vials - at Guerbet three batches each of 400 L and 600 L have been validated regarding

- the manufacturing of bulk solution
- the filling and sterilisation of vials
- the microbiological attributes before sterilisation
- the analysis of the finished product.

Pre-filled syringes –from all three manufacturers 400 L have been validated regarding

- the manufacturing of bulk solution
- the filling and sterilisation of pre-filled syringes
- the microbiological attributes before sterilisation
- the analysis of the finished product.

All manufacturing processes have been adequately validated.

Quality control of drug product

Adequate specifications are applied for the gadoteric acid solution regarding appearance, identification of gadoteric acid (TLC, UV), assay (UV), absorbance, extractable volume, pH, clarity, density, sterility, bacterial endotoxins, free gadolinium, free DOTA, particulate contamination, and identification and assay of meglumine by polarimetry. In general the drug product specifications are adequate and all involved methods adequately validated. Numerous batch analysis results are available for batches vials from the three manufacturers and numerous batch analysis results for batches pre-filled syringes from two manufacturers. All results met the set specifications.

Stability tests on the finished product

Gadoteric acid solution is a very stable product as shown by the stability studies in long term and accelerated conditions. No degradation is observed either during the manufacture or the shelf-life. The only potential impurities in the finished product are free entities (free DOTA and free Gd). They are tested on a routine basis and results show that there is no arising during storage.

Vials - Applying bracketing three industrial batches each of the extreme sizes has been long-term tested either at 25°C/60% RH or 30°C/65% RH. Numerous pilot-scale and industrial batches have been tested in supportive studies at 25°C-35°C-45°C for 10-15-20-60-100 ml vials during either 24 or 36 months.

The 45°C condition is considered stricter than the usual ICH condition of 40°C/75% RH, herewith it can be accepted that no additional accelerated studies according to ICH have been performed. The results show that gadoteric acid solution remain stable after storage at 25°C/60% RH or at 30°C/65% RH. All tested parameters remain in compliance with the specifications regardless the volume of the container. In addition, the product is stable independently of the fill volume. In the 45°C studies, regardless of the dosage form, temperature or storage time, all tested parameters remained in compliance with the specifications. Herewith for the 5-10-15-20-60-100 ml vials a shelf-life of 3 years without specific storage condition can be accepted.

Prefilled syringes - Applying bracketing three industrial batches each of the extreme sizes has been long-term tested either at 25°C/60% RH. Data on pre filled syringes after storage during 6 months at 40°C/75 % RH are provided. In supportive studies additional pilot-scale batches of PFS were tested at temperatures of 25, 35 and 45°C. The results show that gadoteric acid solution remains stable after storage at 25°C/60% RH. All tested parameters remain in compliance with the specifications regardless the volume of the container. In addition, the product is stable independently of the fill volume. In the accelerated and 45°C studies, regardless of the dosage form, temperature or storage time, all tested parameters remained in compliance with the specifications. For the 10-15-20 ml pre-filled syringes a shelf-life of 3 years when stored out of the freezer can be accepted.

Photostability

In addition adequate data on photostability, stability to freeze/thaw and (for the vials) stability after first opening and multiple withdrawals for the large volume vials, are provided. After exposure to light under the conditions described in the ICH guideline, gadoteric acid solution packaged in vials remained stable.

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.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and the USA, respectively.*

II.2 Non-clinical aspects

This product is a generic formulation of Dotarem, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of gadoteric acid released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Gadoteerzuur Guerbet 0.5 mmol/ml in vials/vials for multiple use/pre-filled syringes are parenteral formulations and therefore fulfil 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The qualitative and quantitative composition of Gadoteerzuur Guerbet 0.5 mmol/ml in vials/vials for multiple use/pre-filled syringes are 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.

Risk management plan

The MAH has presented a Risk Management Plan document in the context of Nephrogenic Systemic Fibrosis (dated 29 July 2009, and signed). This RMP was assessed previously during other application procedures.

Product information

SPC

The proposed SPC is in line with the outcome of the recent Art. 31 referral for gadolinium containing products.

Readability test

The MAH has not performed a readability user test on the leaflet of Gadoteric acid but intends to bridge the outcome of the user test of the reference product (Dotarem NL/H/0381/001-006). This approach is considered acceptable as the active substance of both products is the same. The MAH provided a document in which both leaflets have been compared on a basic, key safety message and differences level to evaluate the bridging possibilities for the parent leaflet test results to the daughter leaflet. From this comparison it can be concluded that the outcome of the user test of the reference product can also apply to the leaflet of Gadoteric acid. The RMS agrees with the conclusions and is of the opinion that a new readability user test is not necessary.

For the renewal procedure in 2008 of the reference product Dotarem a successful readability test has been performed. This report has been provided with the application for Gadoteric acid. The conclusions in the renewal assessment report were:

There were sufficient questions about the critical sections. The questions cover the areas, locate information in the package leaflet, understand it and know how to act on it. In the test report four scoring categories were used for traceability: very easy and easy, fairly difficult, very difficult and a given answer is correct or incorrect.

After a pilot test with 3 subjects, two rounds with 10 subjects were undertaken. They were spread on age, sex and education quotas. The participants should have experience with MRI (Magnetic Resonance Imaging) examinations and, because of this, have already had gadoteric acid administration to them or he should be able to imagine a situation in which he would have to take a similar substance.

Information was provided about the time for the interview, the maximum interview time was 1 hour. All interviews were held by an experienced and trained researcher.

*Mean value for information found: 98.2%. Mean value for information understood **by all participants**: 99.6%. The results of the interviews showed that the PIL for DOTAREM 0.5 mmol/ml Solution for injection in vials could be rated as legible and comprehensible according to the requirements of the European directive with a Dependent Readability Index of 96.1 and an Independent Readability Index of 97.9. The Readability Index Ratio is 0.98. This result substantiates the usability of this PIL.*

The user test is found to be acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Gadoteerzuur Guerbet 0.5 mmol/ml in vials/vials for multiple use/pre-filled syringes have a proven chemical-pharmaceutical quality and are generic forms of insert name of Dotarem 0.5 mmol/ml, solution for injection. Dotarem 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 in an aqueous solution, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gadoteerzuur Guerbet 0.5 mmol/ml in vials/vials for multiple use/pre-filled syringes with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 21 July 2011. Gadoteerzuur Guerbet 0.5 mmol/ml in vials, vials for multiple use and pre-filled syringes were authorised in the Netherlands on 31 August 2011.

The date for the first renewal will be: May 2014.

The following post-approval commitments have been made during the procedure:

Quality – Medicinal product - Vials

- The MAH has committed to place one batch per year for vial presentation in stability under long term stability conditions.

Pharmacovigilance system

- The MAH committed to bring the PI of the generic product as well as the reference product in line with the outcome of the pending PSUR WS procedure NL/H/PSUR/0007/002 for all gadoteric acid containing products administered intravenously.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BHT	Butylated hydroxytoluene
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
ICP-MS	Inductive Coupled Plasma - Mass Spectrometry
ICP-AES	Inductive Coupled Plasma - Atomic Emission Spectrometry
IPC	In-process controls
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _½	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached