SUMMARY OF PRODUCT CHARACTERISTICS
(DE/H/4015/002/DC)

1. NAME OF THE MEDICINAL PRODUCT

CYCLOLUX 0.5 mmol/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 279.32 mg gadoteric acid (as meglumine salt), equivalent to 0.5 mmol.

60 ml solution for injection contain 16759.2 mg gadoteric acid (as meglumine salt), equivalent to 30 mmol.
100 ml solution for injection contain 27932 mg gadoteric acid (as meglumine salt), equivalent to 50 mmol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to yellow solution.

Contrast medium concentration	279.32 mg/ml 0.5 mmol/ml
Osmolality at 37°C	1.35 Osm/kg H_2O
Viscosity at 37°C	1.8 mPas
pH value	6.5 – 8.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

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.

Cyclolux should be used only when diagnostic information is essential and not available with unenhanced magnetic resonance imaging (MRI).

4.2 Posology and method of administration

The lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight, and should not exceed the recommended dose per kilogram of body weight detailed in this section.

Posology

Encephalic and spinal MRI:
In neurological examinations, the dose can vary from 0.1 to 0.3 mmol/kg BW, corresponding to 0.2 to 0.6 ml/kg BW. After administration of 0.1 mmol/kg BW to patients with brain tumors, the additional dose of 0.2 mmol/kg BW may improve tumor characterisation and facilitate therapeutic decision making.

MRI of other organs and Angiography:
The recommended dose for intravenous injection is 0.1 mmol/kg (i.e. 0.2 ml/kg) to provide diagnostically adequate contrast.
Angiography: In exceptional circumstances (e.g. failure to gain satisfactory images of an extensive vascular territory) administration of a second consecutive injection of 0.1 mmol/kg BW, equivalent to 0.2 ml/kg BW may be justified. However, if the use of 2 consecutive doses of Cyclolux 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.

Special populations

Impaired renal function
The adult dose applies to patients with mild to moderate renal impairment (GFR $\geq$ 30 ml/min/1.73m^2).

Cyclolux should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use Cyclolux, the dose should not exceed 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Cyclolux injections should not be repeated unless the interval between injections is at least 7 days.

Elderly (aged 65 years and above)
No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Impaired hepatic function
The adult dose applies to these patients. Caution is recommended, especially in the case of perioperative liver transplantation period (see above impaired renal function).

Paediatric population

The 0.1 mmol/kg BW dose applies to all indications except angiography.

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Cyclolux should only be used in these patients after careful consideration at a dose not exceeding 0.1 mmol/kg body weight. More than one dose should not be used during a scan. Because of the lack of information on repeated administration, Cyclolux injections should not be repeated unless the interval between injections is at least 7 days.

Cyclolux is not recommended for angiography in children under 18 years of age due to insufficient data on efficacy and safety in this indication.

Use for whole body MRI is not recommended in children less than 6 months of age.

Method of administration

The product is indicated for intravenous administration only.
Infusion rate: 3-5 ml/min (higher infusion rates up to 120 ml/min, i.e. 2 ml/sec, may be used for angiographic procedures)
Optimal imaging: within 45 minutes after injection
Optimal image sequence: T1-weighted
Intravascular administration of contrast media should, if possible, be done with the patient lying down. After

the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of undesirable effects occur within this time.

The rubber stopper must be punctured only once with an adequate withdrawal device (spike).
In general, the withdrawal device must have the following features: trocar, sterile air filter, luer and a protective sealing stopper.
It can be used with a manual single use (sterile) syringe filled in order to perform a single dosing protocol or in order to inject a second contrast bolus if clinically necessary.
An automatic injection system can be used only for a single patient in order to perform repeated administrations.
At the end of the examination session, quantities of product remaining in the bottle and in the disposable device must be discarded maximum 24 hours after puncture of the rubber stopper. The manufacturer's instructions for the device used must be carefully followed.

The solution for injection should be inspected visually prior to use. Only clear solutions free of visible particles should be used.

4.3 Contraindications

Hypersensitivity to gadoteric acid, to meglumine or to any medicinal products containing gadolinium.

4.4 Special warnings and precautions for use

Gadoteric acid must not be administered by subarachnoid (or epidural) injections.

The usual precaution measures for MRI examination should be taken, such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants, or suspected intracorporal metallic foreign bodies, particularly in the eye.

Hypersensitivity

- As with other gadolinium containing contrast media, hypersensitivity reactions can occur (see "4.8 Undesirable effects"). Most of these reactions appear within at least half an hour after injection of the contrast medium. However, as with other contrast media of this class, the occurrence of delayed reactions up to several days cannot be excluded.
- Patients with hypersensitivity or a previous reaction to contrast media are at increased risk of having a severe reaction. Patients should be questioned for a history of allergy (e.g. hay fever, hives, asthma...) before any contrast medium is injected. In such patients, the decision to use Cyclolux must be made after careful evaluation of the risk-benefit ratio.
- As known from the use of iodinated contrast media, hypersensitivity reactions can be aggravated in patients on beta-blockers, and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.
- During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast medium must be discontinued immediately and - if necessary - specific therapy instituted. A venous access should thus be kept during the entire examination. To permit immediate emergency countermeasures, appropriate drugs (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand.

Impaired renal function

Prior to administration of Cyclolux, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests.

There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30

ml/min/1.73m^2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with Cyclolux, it should therefore only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI.

Haemodialysis shortly after gadoteric acid administration may be useful at removing gadoteric acid from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Elderly

As the renal clearance of gadoteric acid may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction.

Paediatric population

Neonates and infants
Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Cyclolux should only be used in these patients after careful consideration.
In neonates and infants the required dose should be administered by hand.

Cardiovascular disease

In patients with severe cardiovascular disease Cyclolux should only be administrated after careful risk benefit assessment because only limited data are available so far.

CNS disorders

Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures. Precautionary measures should be taken, e.g. close monitoring. All equipment and drugs necessary to counter any convulsions which may occur must be made ready for use beforehand.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other medicinal products have been observed. Formal drug interaction studies have not been carried out.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of gadoteric acid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Cyclolux should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

Breastfeeding

Gadolinium containing contrast agents are excreted into breast milk in very small amounts (see section 5.3). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of Cyclolux, should be at the discretion of the doctor and lactating mother.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take into account that nausea may incidentally occur.

4.8 Undesirable effects

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 and/or pain at the injection site are the most frequently observed reactions.

During clinical trials, headache and paresthesia were very commonly observed (>1/10), and nausea, vomiting and skin reactions such as erythematous rash and pruritus were commonly observed (>1/100 - <1/10).

Since post-marketing, the most commonly reported adverse reactions following administration of gadoteric acid are nausea, vomiting, pruritus and hypersensitivity reactions.

In hypersensitivity reactions, the reactions most frequently observed are skin reactions, which can be localized, extended or generalized.

These reactions occur most often immediately (during the injection or within one hour after the start of injection) or sometimes delayed (one hour to several days after injection), presenting as skin reactions in this case.

Immediate reactions include one or more effects, which appear simultaneously or sequentially, which are most often cutaneous, respiratory and/or cardiovascular reactions. Each sign may be a warning sign of a starting shock and go very rarely to death.

Isolated cases of nephrogenic systemic fibrosis (NSF) have been reported with gadoteric acid, most of which were in patients co-administered other gadolinium-containing contrast agents (see section 4.4).

The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data). The data presented are from clinical trials when available, or from an observational study involving 82,103 patients.

Organ Class System	**Frequency: adverse reaction**
Immune system disorders	Uncommon: hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Psychiatric disorders	Very rare: agitation, anxiety
Nervous system disorders	Very common: paraesthesia, headache Rare: dysgeusia Very rare: coma, convulsion, syncope, presyncope, dizziness, parosmia, tremor
Eye disorders	Very rare: conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased, eyelid edema
Cardiac disorders	Very rare: cardiac arrest, bradycardia, tachycardia, arrhythmia, palpitations
Vascular disorders	Very rare: hypotension, hypertension, vasodilatation, pallor
Respiratory, thoracic and mediastinal disorders	Very rare: respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, pharyngeal oedema, dyspnoea, nasal congestion, sneezing, cough, dry throat
Gastrointestinal disorders	Common: nausea, vomiting Very rare: diarrhoea, abdominal pain, salivary hypersecretion
Skin and subcutaneous tissue disorders	Common: pruritus, erythema, rash Rare: urticaria, hyperhidrosis,

	Very rare: eczema, angioedema Not known: nephrogenic systemic fibrosis
Musculoskeletal and connective tissue disorders	Very rare: muscle contracture, muscular weakness, back pain
General disorders and administration site conditions	Common: feeling hot, feeling cold, injection site pain Very rare: malaise, thoracic pain, chest discomfort, fever, chills, face oedema, asthenia, injection site discomfort, injection site reaction, injection site oedema, injection site extravasation, injection site inflammation (in case of extravasation), injection site necrosis (in case of extravasation), superficial phlebitis
Investigations	Very rare: decreased oxygen saturation

The following adverse reactions were reported with other intravenous contrast agents for MRI :

Organ Class System	**Adverse reaction**
Blood and lymphatic system disorders	Haemolysis
Psychiatric disorders	Confusion
Eye disorders	Blindness transient, eye pain
Ear and labyrinth disorders	Tinnitus, ear pain
Respiratory, thoracic and mediastinal disorders	Asthma
Gastrointestinal disorders	Dry mouth
Skin and subcutaneous tissue disorders	Dermatitis bullous
Renal and urinary disorders	Urinary incontinence, renal tubular necrosis, renal failure acute
Investigations	Electrocardiogram PR prolongation, blood iron increased, blood bilirubin increased, serum ferritin increased, liver function test abnormal

Adverse reaction in Children
Adverse events related to gadoteric acid are uncommon in children. The expectedness of these events is identical to that of the events reported in adults (see section 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

4.9 Overdose

Gadoteric acid can be removed by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: paramagnetic contrast media
ATC code: V08 CA 02 (gadoteric acid).
This product has no specific pharmacodynamic activity and is biologically inert.

Cyclolux 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 $mmol^{-1}Lsec^{-1}$ and on the spin-spin relaxation time (T2) about 4.27 $mmol^{-1}Lsec^{-1}$.

5.2 Pharmacokinetic properties

After intravenous administration gadoteric acid is quickly distributed in the extracellular fluids. The distribution volume was approx. 18 l which is approximately equal to the volume of extra-cellular 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 feces is negligible. No metabolites were detected. The elimination half life amounts to about 1.6 hours in patients with a normal renal function. In renally impaired patients, the elimination half life was increased to approximately 5 hours for a creatinine clearance between 30 and 60 ml/min and approximately 14 hours 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.

In patients with normal renal function, the plasmatic half life is about 90 minutes. It is eliminated by glomerular filtration in unchanged form.

The plasmatic clearance is reduced in case of renal impairment.

Gadoteric acid is poorly excreted in the milk and cross slowly through the placenta barrier.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.
Animal studies have shown negligible (less than 1 % of the administered dose) secretion of gadoteric acid in maternal milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Meglumine
Dota
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Chemical and physical in-use stability has been demonstrated for 72 hours at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage

times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8° C, unless opening has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 and 10 Type II single-use colourless glass vials of 60 ml and 100 ml, sealed with a stopper of bromobutyl rubber and packed in unit carton box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The peel-off tracking label on the vials should be stuck onto the patient record to enable accurate recording of the gadolinium contrast agent used. The dose used should also be recorded. If electronic patient records are used, the name of the product, the batch number and the dose should be entered into the patient record.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanochemia Pharmazeutika AG
Boltzmanngasse 11
1090 Vienna, Austria

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: <{DD/MM/YYYY}> <{DD month YYYY}>
Date of last renewal: <{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

<[To be completed nationally]>