1. NAME OF THE MEDICINAL PRODUCT

DOTAGRAF 0.5 mmol/ml solution for injection in vials

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 1 ml of solution :

Gadoteric acid[1)] ……...…… 279.32 mg

Corresponding to Gadolinium (III) oxide …… 90.62 mg
Corresponding to DOTA……. 202.46 mg

Contrast agent concentration: …… 0.5 mmol/mL

[1)]Gadoteric acid: complex of gadolinium oxide with 1, 4, 7, 10 tetraazacyclododecane-N,N',N'',N''' tetraacetic acid (DOTA).

10ml solution for injection contain 2793.2 mg gadoteric acid (as meglumine salt), equivalent to 5 mmol.
20ml solution for injection contain 5586.4 mg gadoteric acid (as meglumine salt), equivalent to 10 mmol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in vials.
Clear, colourless to yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Nuclear magnetic resonance imaging:

- Neuroradiology: tumour of the spine and the surrounding tissues, intracranial tumours.
- Abdominal radiology: primary and secondary tumours.
- Primary tumour of the bone and soft tissues.

4.2 Posology and method of administration

Posology

Adults

The recommended dose is 0.1 mmol/kg, i.e. 0.2 mL/kg, in adults.

Special populations

Impaired renal function

The adult dose applies to patients with mild to moderate renal impairment (GFR ≥ 30 ml/min/1.73m^2).

Dotagraf 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 Dotagraf, 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, Dotagraf 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 (2-18 years)

MRI of brain and spine / whole-body MRI: the recommended and maximum dose of Dotagraf is 0.1 mmol/kg body weight. More than one dose should not be used during a scan.

Method of administration
The product is indicated for intravenous administration only.
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.

Prepare a syringe with a needle. Remove the plastic disk. After cleaning the stopper with a pad soaked in alcohol, puncture the stopper with the needle. Withdraw the quantity of product required for the examination and inject it intravenously.
For single use only, any unused solution should be discarded.
The solution for injection should be inspected visually prior to use. Only clear solutions free of visible particles should be used.

Paediatric population *(2-18 years)*
Depending on the amount of Dotagraf to be given to the child, it is preferable to use Dotagraf vials with a single use syringe of a volume adapted to this amount in order to have a better precision of the injected volume.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Do not use by intrathecal route. Take care to maintain strictly intravenous injection: extravasation may result in local intolerance reactions, requiring the usual local care.

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, including life-threatening (see section 4.8). Hypersensitivity reactions may be either allergic (described as anaphylactic

reactions when serious) or non allergic. They can be either immediate (less than 60 minutes), or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often unpredictable.

- There is always a risk of hypersensitivity regardless of the dose injected.
- Patients who have already experienced a reaction during previous administration of a gadolinium-containing MRI contrast agent present an increased risk of experiencing another reaction on subsequent administration of the same product, or possibly other products, and are therefore considered to be at high risk.
- The injection of gadoteric acid may aggravate symptoms of an existing asthma. In patients with asthma unbalanced by the treatment, the decision to use gadoteric acid 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.
- Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to contrast media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions and premedication with antihistamines and/or glucocorticoids may be considered.
- 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 Dotagraf, 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 Dotagraf, 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.

Cardiovascular disease

In patients with severe cardiovascular disease Dotagraf 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.

Accumulation of gadolinium in the brain

The current evidence suggests that gadolinium may accumulate in the brain after multiple administration of GBCAs.
Increased signal intensity on non-contrast T1-weighted images of the brain has been observed after multiple administrations of GBCAs in patients with normal renal function. Gadolinium has been detected in brain tissue after multiple exposures to GBCAs, particularly in the dentate nucleus and globus pallidus. The evidence suggests that the risk of gadolinium accumulation is higher after repeat administration of linear than after repeat administration of macrocyclic agents.
The clinical significance of gadolinium accumulation in the brain is presently unknown. In order to minimise potential risks associated with gadolinium accumulation in the brain, it is recommended to use the lowest effective dose and perform a careful benefit risk assessment before administering repeated doses.

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.

Concomitant medications to be taken into account

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists: these medicinal products decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders: the radiologist must be informed before injection of gadolinium complexes, and resuscitation equipment must be at hand.

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). Dotagraf should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

Lactation

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 Dotagraf, 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. Injection site reations, nausea and headache are the most frequently observed reactions.
During clinical trials, nausea, headache, injection site reactions, feeling cold, hypotension, somnolence, dizziness, feeling hot, burning sensation, rash, asthenia, dysgeusia and hypertension were the most frequent, uncommonly observed (≥1/1000 to <1/100) related adverse events.

Since post-marketing, the most commonly reported adverse reactions following administration of gadoteric acid have been 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 goes 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 involving 2822 patients when available, or from a pool of observational studies involving 185,500 patients.

Organ Class System	**Frequency: adverse reaction**
Immune system disorders	Uncommon: hypersensitivity, Very rare: anaphylactic reaction, anaphylactoid reaction
Psychiatric disorders	Rare: anxiety Very rare: agitation
Nervous system disorders	Uncommon: headache, dysgeusia, dizziness, somnolence, paraesthesia (including burning sensation) Rare: presyncope Very rare: coma, convulsion, syncope, tremor, parosmia
Eye disorders	Rare: eyelid edema Very rare: conjunctivitis, ocular hyperaemia, vision blurred, lacrimation increased
Cardiac disorders	Rare: palpitations Very rare: tachycardia, cardiac arrest, arrhythmia, bradycardia
Vascular disorders	Uncommon: hypotension, hypertension Very rare: pallor, vasodilatation
Respiratory, thoracic and mediastinal disorders	Rare: sneezing Very rare: cough, dyspnoea, nasal congestion, respiratory arrest, bronchospasm, laryngospasm, pharyngeal oedema, dry throat, pulmonary oedema
Gastrointestinal disorders	Uncommon: nausea, abdominal pain Rare: vomiting, diarrhoea, salivary hypersecretion
Skin and subcutaneous tissue disorders	Uncommon: rash Rare: urticaria, pruritus, hyperhidrosis, Very rare: erythema, angioedema, eczema Not known: nephrogenic systemic fibrosis
Musculoskeletal and connective tissue disorders	Very rare: muscle cramps, muscular weakness, back pain
General disorders and administration site conditions	Uncommon: feeling hot, feeling cold, asthenia, injection site reactions (extravasation, pain, discomfort, oedema, inflammation, coldness) Rare: chest pain, chills Very rare: malaise, chest discomfort, pyrexia, face oedema,

	injection site necrosis (in case of extravasation), phlebitis superficial
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
Safety of paediatric patients was considered in clinical trials and postmarketing studies. As compared to adult, the safety profile of gadoteric acid did not show any specificity in children. Most of reactions are gastrointestinal symptoms or signs of hypersensitivity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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.

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)

Contrast medium concentration:	279.32 mg/ml 0.5 mmol/ml
Osmolality at 37°C	1350 mOsm/kg H_2O
Viscosity at 20°C	3.2 mPa.s
Viscosity at 37°C	2.0 mPa.s
pH	6.5 -8.0

Dotagraf 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.
The current evidence suggests that gadolinium may accumulate in the brain after repeated administration of GBCAs although the exact mechanism of gadolinium passage into the brain has not been established.

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

DOTA
Meglumine
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.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

10 ml and 20 ml injection clear glass vial (Ph. Eur. Type II glass container, moulded glass). Closure: Rubber closures are made of bromobutyl (Ph.Eur.). Seal: aluminium caps with a plastic polypropylene (PP) flip off lid. Packed in a unit carton box of 10 vials.
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. MANUFACTURER

Sanochemia Pharmazeutika GmbH
Landeggerstraβe 7
2491 Neufeld an der Leitha
AUSTRIA

8. DATE OF REVISION OF THE TEXT

13-July-2020