SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dotagraf 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.

10 ml solution for injection contain 2793.2 mg gadoteric acid (as meglumine salt), equivalent to 5 mmol.
15 ml solution for injection contain 4189.8 mg gadoteric acid (as meglumine salt), equivalent to 7.5 mmol.
20 ml 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.
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.

Dotagraf is a contrast agent indicated for enhancement of the contrast in Magnetic Resonance Imaging (MRI) for a better visualization/delineation in:

Adult and paediatric population (0-18 years)
- 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.

Adult population
- MR angiography including lesions or stenoses of the non-coronary arteries.

Dotagraf should be used only when diagnostic information is essential and not available with unenhanced

MRI.

4.2 Posology and method of administration

Posology

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.

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.

Whole body MRI and Angiography

The recommended dose for intravenous injection is 0.1 mmol/kg BW (i.e. 0.2 ml/kg BW) 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 Dotagraf is anticipated prior to commencing angiography, use of 0.05 mmol/kg BW, equivalent to 0.1 ml/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 ≥ 30 ml/min/1.73 m^2).

Dotagraf should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73 m^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

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

Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, Dotagraf 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, Dotagraf injections should not be repeated unless the interval between injections is at least 7 days.

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

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.

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
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.
In neonates and infants the required dose should be administered by hand.

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 used intrathecally. Serious, life-threatening and fatal cases, primarily with neurological reactions (e.g. coma, encephalopathy, seizures), have been reported with intrathecal use.
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/1.73 m^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.

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, Dotagraf should only be used in these patients after careful consideration.

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.

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
Data from the use of gadolinium-based contrast agents including gadoteric acid in pregnant women is limited. Gadolinium can cross the placenta. It is unknown whether exposure to gadolinium is associated with adverse effects in the foetus. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Gadoteric acid crosses the placenta slowly. Dotagraf should not be used during pregnancy unless the clinical condition of the woman requires use of gadoteric acid.

Breast-feeding
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 reactions, nausea and headaches 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 (≥1/1,000 to <1/100) related adverse events.

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, gastrointestinal, articular and/or cardiovascular reactions. Each sign may be a warning sign of a starting shock and leads 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 (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), 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: presyncopeVery 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, eczemaNot 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.

Kuwait: Drug &Food Control, Ministry of Health Tel.: +965-24811532 Fax: +965-24811507 Email : Adr_reporting@moh.gov.kw Website: Website: http://eservices.moh.gov.kw/SPCMS/DrugCmp.aspx	**Egypt:** Egyptian Pharmaceutical Vigilance Centre Hotline: 15301 Email: pv.followup@edaegypt.gov.eg Website: www.edaegypt.gov.eg
United Arab Emirates (UAE): Pharmacovigilance & Medical Device section Tel: 80011111 / +971 42301000 Email: pv@mohap.gov.ae Website: www.mohap.gov.ae P.O.Box 1853 Dubai	**Jordan:** Tel: +962-6-5632000 JFDA email : jpc@jfda.jo JFDA website: www.jfda.jo http://primaryreporting.who-umc.org/JO
Other Countries: Please contact the relevant competent authority	

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: V08CA02 (gadoteric acid).

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-1,4,7,10-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 $mmol^{-1} \cdot L \cdot sec^{-1}$ and on the spin-spin relaxation time (T2) about 4.27 $mmol^{-1} \cdot L \cdot sec^{-1}$.

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.

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
1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (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

Do not store above 30°C.

6.5 Nature and contents of container

1 and 10 Type II single-use colourless glass vials of 10 ml and 20 ml (filled to 15 or 20 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

Bayer AG,
51368 Leverkusen, Germany.
Manufacturer
Sanochemia Pharmazeutika GmbH
Landegger Strase 7
2491 Neufeld/Leitha, Austria.

8. DATE OF REVISION OF THE TEXT

07/2024

This is a medicament

- A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists