PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAME (AND DOSAGE FORM)

DOTAREM® (Sterile solution for injection)

DOTAREM® PREFILLED SYRINGES (Sterile solution for injection)

COMPOSITION

Gadoteric acid (Gd-DOTA) 27,932 g/100 ml (0,5 mmol/l) corresponding to 20,246 g/100 ml DOTA (1,4,7,10-tetra-azacyclododecane-N,N',N",N"'-tetra-acetic acid) and 9,062 g/100 ml gadolinium oxide.

Osmolality: 1350 mOsm/kg

Viscosity at 20 ºC: 3,2 mPa.s

Viscosity at 37 ºC: 2,0 mPa.s

pH: 6,5 – 8,0

Inactive ingredients: meglumine, water for injections

PHARMACOLOGICAL CLASSIFICATION

A28 Contrast media

PHARMACOLOGICAL ACTION

DOTAREM is a paramagnetic contrast medium for magnetic resonance imaging (MRI). Gadoteric acid is formed by complexing of the paramagnetic ion, gadolinium with 1,4,7,10-tetra-azacyclododecane-N,N',N",N"'-tetra-acetic acid (DOTA). The presence of 7 unpaired electrons of the gadolinium ion Gd^{3+}, attributes to the string paramagnetic properties, with a shortening of the T_1 longitudinal relaxation time. This results in an increased signal intensity in T_1-weighted sequences and reduced signal intensity in T_2-weighted sequences in the magnetic resonance imaging.

Gadoteric acid has paramagnetic properties which increase contrast enhancement in magnetic resonance images. It has no specific pharmacodynamic activity and is biologically inert.

Pharmacokinetics

Pharmacokinetic studies indicate that DOTAREM is distributed in the extracellular fluids, does not cross the blood-brain barrier, does not bind to albumin and is rapidly eliminated in an unchanged form by glomerular filtration. In patients with normal renal function, the plasma half-life is approximately 90 minutes. It is eliminated by glomerular filtration in unchanged form.

Plasma clearance is retarded in the event of renal failure. Gd-DOTA excretion in breast milk is low and crossing of the placental barrier is low.

INDICATIONS

Enhancement of contrast in magnetic resonance imaging.

Encephalic and spinal pathologies:

- Brain tumours
- Tumours of the spine and the surrounding tissue
- Intervertebral disk prolapsed
- Infectious diseases

Abdominal pathologies:

- Primary and secondary liver tumours

Osteo-articular pathologies:

- Bone and soft tissue tumours
- Synovial diseases

Angiography

CONTRAINDICATIONS

Hypersensitivity to any of the components.

Contraindications related to magnetic resonance imaging (MRI): patients with vascular clips, pacemakers.

WARNINGS AND SPECIAL PRECAUTIONS

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

Administer only by strict intravenous injection. In the event of extravasation, local intolerance reactions can occur, which require conventional local treatment.

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

Hypersensitivity

- As with other gadolinium containing contrast media, hypersensitivity reactions can occur (see "Side 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 media is injected. In such patients, the decision to use DOTAREM 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.
- If hypersensitivity reactions occur, administration of the contrast media 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.
- Caution should be exercised in patients with severe renal failure or impaired renal function.
- There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR < 30 ml/min/1,73 m^2). As there is possibility that NSF may occur with DOTAREM, it should only be used in these patients after careful consideration.

During the examination, the following are required:

- surveillance by a physician.

- maintenance of an intravenous route for emergency treatment in the event of a reaction.

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 convulsions, which may occur, must be made ready for use beforehand.

It is of decisive importance for prompt action in the event of contrast medium incidents to be familiar with the practice of emergency measures. To permit immediate counter-measures to be taken in emergencies, appropriate medicines and instruments (e.g. endotracheal tube and ventilator) should be readily available.

INTERACTIONS

No interactions have been reported.

PREGNANCY AND LACTATION

Although no teratogenic effects have been observed in animals to date, the safety of DOTAREM in human pregnancy and lactating women has not been demonstrated.

DOSAGE AND DIRECTIONS FOR USE

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.

The recommended dose is 0,2 ml/kg in adults and in children.

In angiography, depending on the results of the examination performed, a second injection of 0,2 ml/kg in adults may be administered during the same session if necessary.

The product is intended for intravenous administration only.

SIDE EFFECTS

Side effects in association with the use of DOTAREM are usually mild to moderate in intensity and transient in nature. A sensation of heat, cold and/or pain at the injection site is the most frequently observed reaction.

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

However, rare anaphylactoid reactions have been reported that may be very rarely severe, life-threatening or have a fatal outcome, particularly in patients with a history of allergy. These allergoid reactions can occur irrespective of the amount administered and the mode of administration and may take the form of one or more of the following symptoms: angioedema, anaphylactic shock, circulatory and cardiac arrest, hypotension, larynx oedema, bronchospasm, laryngospasm, pulmonary oedema, dyspnoea, stridor, coughing, pruritus, rhinitis, sneezing, conjunctivitis, urticaria and rash. Some of these symptoms may be the first signs of incipient state of anaphylactic shock. Delayed contrast medium reactions are possible.

Since post-marketing, the following adverse reactions have been reported:

General disorders and administration site conditions:

Very rarely (< 0,01 %): chest pain, back pain, malaise, fever, sweating increased, coldness, pallor and syncope.

While injecting DOTAREM into veins with a small lumen, there is the possibility of adverse effects such as redness and swelling. In case of extra vascular injection local tissue pain may occur. Cases of superficial phlebitis, possibly related to the injection technique, have been rarely reported.

Respiratory, thoracic and mediastinal disorders:

Very rarely (< 0,01 %): respiratory disorders.

Gastrointestinal disorders:

Very rarely (< 0,01 %): abdominal pain.

Skin and subcutaneous tissue disorders:

Very rarely (< 0,01 %): eczema, erythema, urticaria, pruritus and rash.

Nervous system disorders:

Very rarely (< 0,01 %): dizziness, generalized convulsions, tremor, fatigue and somnolence.

Musculoskeletal, connective tissue and bone disorders:

Very rarely (< 0,01 %): muscle cramps, muscle weakness.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See “Side effects”. Treatment is symptomatic and supportive.

IDENTIFICATION

A clear colourless to yellow solution.

PRESENTATION

DOTAREM sterile solution for injection is available in clear glass vials containing 5 ml, 10 ml, 15 ml, 20 ml, 60 ml and 100 ml and DOTAREM PREFILLED SYRINGES in 10 ml, 15 ml and 20 ml glass or plastic prefilled syringes.

DOTAREM sterile solution for injection and DOTAREM PREFILLED SYRINGES are sold as single units or as 10 units per pack.

Not all pack sizes are marketed at any one time.

STORAGE INSTRUCTIONS

Store at or below 30 ºC. Protect from light.

Do not freeze prefilled syringes.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

DOTAREM: 31/28/0550

DOTAREM PREFILLED SYRINGES: 31/28/0551

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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