Hexabrix 320

Meglumine/sodium ioxaglate 320 mg iodine/mL

Presentation

Hexabrix 320

Glass bottles containing a sterile solution of meglumine ioxaglate 39.30% w/v and sodium ioxaglate 19.65% w/v containing 320 mg iodine in combined form per ml. The solution is a light yellow colour. The aqueous solution also contains sodium calcium edededate BP 0.01% w/v.

Uses

Pharmacokinetics

Hexabrix 320 is rapidly eliminated by the kidneys with a half-life of about 90 minutes. 99% of the dose is eliminated in 24 hours. Biliary excretion may be of some importance in kidney impairment. The compound is not metabolised.

Indications

This medicinal product is for diagnostic use only in adults and children.

Low osmolar X-ray contrast medium for the opacification of the vascular system, urinary tract, joints and female genital tract, the indications for which are given below.

Dosage and Administration

For ease of injection it may be found helpful to warm Hexabrix 320 to near body temperature.

Femoral and other peripheral arteriographies

15-20 mL injected into the femoral or iliac artery will produce excellent visualisation of the arterial tree of the leg. A similar or smaller dose is indicated for smaller arteries.

Cerebral angiography (carotid and vertebral)

Average adult dose 6 - 8 mL for each injection. Up to 10 injections each of 8 mL may be required.
**Angio-cardiography**

Multiple small test injections may be used for positioning catheter tip.

**Adults and Children over 14 years**

30-50 mL per injection.

**Children (14 years and under) and infants**

1-1.5 mL per kg bodyweight.

Multiple injections may be required. Total dosage should not normally exceed 4 mL per kg bodyweight. In exceptional circumstances, this total dose may be exceeded according to the clinical condition.

**Abdominal aortography (direct puncture or catheterisation)**

**Adults**

20-30 mL.

Up to 50 mL may be used particularly if films of the legs are also taken following the same injection.

**Thoracic aortography (including arch aortography)**

**Adults and Children**

0.5-1.0 mL per kg bodyweight up to 40 mL per injection.

This may be repeated if necessary. Total dosage should not normally exceed 4 mL per kg bodyweight.

**Pulmonary angiography**

**Adults**

20-40 mL.

**Children**

0.5-1.0 mL per kg bodyweight.

Special care should be exercised in patients with pulmonary arterial hypertension.

**Coronary arteriography**

**Adults**

3-8 mL per injection depending on size of artery.

Several injections are usually given for complete demonstration particularly in the left coronary artery.

**Digital subtraction angiography**

Dilute 50% with Water for Injection BP or Sodium Chloride and Dextrose Injection BP to produce a solution containing 160 mg iodine per mL. The appropriate volume of diluted medium (depending on part of the body to be visualised) should be injected into a suitable artery.

**Intravenous aortography**
Adults and Children
1.0 - 1.5 mL per kg bodyweight.
In adults 100 mL is often used; frequently this amount is subdivided equally and given by simultaneous rapid bilateral injection.

**Femoral venography**
**Adults**
20-50 mL and/or inferior vena cavography.

**Leg phlebography**
**Adults**
20-50 mL injected into a vein in the foot.

**Intravenous urography**
**Adults**
20-80 mL.
60-100 mL may be used provided that the patient is not dehydrated.

**Children Under 12 kg**
2 mL per kg bodyweight.

**Children Over 12 kg**
1.5 mL per kg bodyweight (with a minimum of 24 mL).

**Children over 10 years of age**
Lower range of adult dosage.

Patients with severe renal disease or diabetes should be well hydrated. Particular care is necessary in these patients as temporary deterioration in renal function has been reported.

**Splenography portal venography**
**Adults**
20-40 mL by splenic puncture.

**Knee arthography (double contrast)**
**Adults**
By injection into the knee joint. 4.5 mL together with injections of air before and after the positive contrast medium.

**Hysterosalpingography**
About 10 mL are usually required, administered by slow injection into the uterine cervical canal via a syringe and suitable cannula, preferably under fluoroscopic control.

**Special Populations**
Elderly
Since a decline in physiological functions is common in the elderly, the clinical condition of the patient should be carefully monitored. Hexabrix 320 should be administered with caution, in well hydrated patients and the administered dose reduced to the minimum.

Children
Particular attention should be paid to the injection sites of neonates and infants. The administered dose should be reduced to the minimum.

Impaired renal function:
In patients with severe renal insufficiency or diabetes, Hexabrix 320 should be administered with caution in well hydrated patients and the administered dose should be reduced to the minimum.

Contraindications
- Hypersensitivity to ioxaglic acid or any of the excipients
- Manifest hyperthyroidism or thyrotoxicosis
- Hysterosalpingography during pregnancy or in the presence of acute inflammatory processes in the pelvic region
- Epidural and intrathecal administration (can cause convulsions and result in death).

Special warnings and precautions for use
- There is a risk of allergic reactions whatever the administration route or dose.
- The risk of intolerance is not completely ascertainable with products administered locally to enhance contrast in body cavities:
  - Administration via particular routes (articular, biliary, intra-uterine etc) results in appreciable systemic absorption, i.e. systemic effects may be observed
  - However, the allergic immune mechanism is not dose-dependent and immuno-allergic reactions may be observed at any time, whatever the administration route.

General comments for all iodinated contrast agents

Warnings
Myelography is not an indication for Hexabrix 320.

The examination should only be initiated after insertion of an indwelling venous catheter.

All iodinated contrast agents may cause minor or major reactions that may be life-threatening or even fatal. They may be immediate (within 60 minutes) or delayed (up to 7 days). They are often unpredictable but they occur more frequently in patients with a
history of hypersensitivity reactions to earlier examinations with iodinated contrast media. Premedication is recommended for these patients.

The risk of a major reaction implies that emergency measures must be immediately available especially in patients on beta blockers in whom adrenaline and vascular perfusion would be insufficiently effective.

Sufficient fluid intake (no dehydration) and normal electrolyte balance must be ensured in elderly patients, infants, small children, patients with renal damage (oliguria, polyuria) or hyperuricemia, multiple myeloma, patients with plasmacytoma or diabetes mellitus, particularly if it is longstanding.

**Iodinated contrast agents and the thyroid**

Before administering an iodinated contrast agent, make sure that the patient is not scheduled for a scintigraphic examination or laboratory tests related to the thyroid or for administration of radioactive iodine for therapeutic purposes.

Administration of contrast agents via any route affects hormone tests and iodine uptake by the thyroid or by metastases of thyroid cancer, until urinary excretion of iodine returns to normal.

**Precautions for use**

*Intolerance to iodinated contrast agents*

Before the examination:
- Identify subjects at risk by a precise interview on their history
- Corticosteroids and H1-type antihistamines have been suggested as premedication in patients at risk for intolerance reactions (history of intolerance to an iodinated contrast agent). However, they do not prevent the occurrence of serious or fatal anaphylactic shock.

Throughout the examination, maintain:
- Medical monitoring
- An indwelling intravenous catheter

After the examination:
- After contrast agent administration, the patient must be monitored for at least 30 minutes
- The patient must be informed of the possibility of delayed reactions (for up to seven days (See Adverse reactions section).

**Renal failure**

Iodinated contrast agents can induce a transient deterioration of renal function or exacerbate pre-existing renal failure. The preventive measures are as follows:
- Identify patients at risk, i.e. patients who are dehydrated or who have renal failure, diabetes, severe heart failure, monoclonal gammopathy (multiple myeloma,
Waldenstrom’s macroglobinemia), hyperuricemia, a history of renal failure after administration of iodinated contrast agents, children under 1 year of age and elderly atheromatous subjects

- Hydrate with appropriate water and sodium replenishment if necessary
- Avoid combinations with nephrotoxic medicines (if such a combination is necessary, laboratory monitoring of renal function must be intensified. The medicines concerned are in particular the aminoglycosides, organoplatinums, high dose of methotrexate, pentamidine, foscarnet and certain antiviral agents (aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir), vancomycin, amphotericin B, immunosuppressors such as cyclosporine or tacrolimus, ifosfamide)
- Allow at least 48 hours between radiological examinations with contrast agent injections, or delay further examinations until renal function returns to baseline
- Check for lactic acidosis in diabetics treated with metformin, by monitoring serum creatinine. Normal renal function: discontinue metformin for at least 48 hours after contrast agent administration or until renal function returns to normal. Abnormal renal function: metformin is contraindicated. In emergencies, if the examination is required, precautions must be taken, i.e. discontinue metformin, hydrate the patient, monitor renal function and test for signs of lactic acidosis.

Iodinated contrast agents can be used in haemodialysed patients as the agents are removed by dialysis. Prior approval should be obtained from the haemodialysis department.

**Hepatic failure**

Particular attention is required if the patient has both hepatic and renal failure, which increases the risk of contrast agent retention.

**Asthma**

Asthma should be stabilised before injecting the iodinated contrast agent.

Particular attention is required if the asthmatic attack has occurred within eight days prior to the examination, because of the increased risk of bronchospasm.

**Dysthyroidism**

Following injection of iodinated contrast agent, particularly in patients with goitre or a history of dysthyroidism, there is a risk of either an episode of hyperthyroidism or induction of hypothyroidism. There is also a risk of hypothyroidism in neonates who have received, or whose mother has received, an iodinated contrast agent. In such population, screening for hypothyroidism should be performed systemically after administration of the product to neonates and particularly to premature babies by assaying TSH and possibly free T4, 7-10 days and 1 month after iodine overload.

**Severe cardiovascular diseases**

In patients with manifest or incipient heart failure, coronary disease, pulmonary hypertension, or valvular heart disease, the risks of pulmonary oedema, myocardial ischaemia and arrhythmia and severe haemodynamic disturbances is increased after the administration of an iodinated contrast agent.
Post-marketing case of Torsade de Pointes have been reported in patients using sodium and meglumine ioxaglate, hence Hexabrix 320 should be administered with caution to patients who have or may develop prolongation of QTc, including patients taking other medicines that lead to QT prolongation.

**Central nervous system disorders**

The benefit-to-risk ratio must be evaluated for each case:

- Due to the increased risk of neurological symptoms in patients manifesting a transient ischaemic attack, stroke, recent intracranial bleeding, cerebral oedema or idiopathic or secondary epilepsy (tumour, scar)
- If the intra-arterial route is used in patients who are alcoholic (acute or chronic alcoholism) or addicted to other substances.

**Phaeochromocytoma**

Patients with phaeochromocytoma may suddenly develop hypertension after intravascular administration of a contrast agent, which may require appropriate management before the examination.

**Myasthenia gravis**

Administration of a contrast agent may exacerbate the symptoms of myasthenia gravis.

**Exacerbation of side effects**

Adverse reactions related to administration of iodinated contrast agents may be exacerbated in patients showing agitation, anxiety and pain. Appropriate management may be needed, which may even involve sedation.

**Products administered via the intra-uterine route**

In the interview and with appropriate tests, systematically check for possible pregnancy in women of childbearing age. Exposure of the female genital tract to x-rays calls for a careful evaluation of the benefit-to-risk ratio.

In the event of inflammation or acute pelvic infection, hysterosalpingography can only be performed after a careful assessment of the benefit-to-risk ratio.

Hexabrix 320 contains 352mg of sodium per 100mL. This should be taken into account in patients on a strict low sodium diet.

**Interaction with other medicinal products and other forms of interaction**

**Medicinal products**

Metformin in diabetics (See Precautions for Use – Renal failure section)
Radiopharmaceuticals (See Warnings section)

Iodinated contrast agents may disturb the uptake of radioactive iodine by thyroid tissue for several weeks, which may result in an uptake deficit in thyroid scintigraphy and a reduction of the therapeutic efficacy of iodine 131.

If renal scintigraphy involving the injection of a radiopharmaceutical excreted by the renal tubules is scheduled, it is preferable to perform it before injecting the iodinated contrast agent.

Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor agonists

These medicinal products reduce the efficacy of cardiovascular compensation mechanisms for blood pressure disorders. The physician must be aware of this before injecting the iodinated contrast agent and emergency measures must be available.

Diuretics

Because of the risk of dehydration due to diuretics, rehydration with water and electrolytes must be carried out before contrast agent injection, to limit the risk of acute renal failure, particularly if high doses of iodinated contrast agent were used.

Interleukin-2

Reactions to contrast agents may be increased if the patient has recently been treated with interleukin-2 (intravenous route), i.e. skin eruptions or more rarely hypotension, oliguria, or renal failure.

Other forms of interaction

High concentrations of iodinated contrast agents in plasma and urine may interfere with in vitro tests for bilirubin, proteins and inorganic substances (iron, copper, calcium and phosphate). These tests should not be carried out within 24 hours following the examination.

Thyroid tests (PBI, labelled iodine) are affected for several weeks after administration of iodinated contrast agents. To avoid confusion, thyroid hormones (thyroxine, triiodothyronine) should be assayed directly.

Fertility, pregnancy and lactation

Fertility

Toxicological studies on reproductuve function showed no effects on reproduction and fertility.

Pregnancy

It is preferable to avoid exposure to X-rays during pregnancy.

There are no, or limited amount of data from the use of ioxaglic acid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Hexabrix 320 should not be used during pregnancy unless the clinical condition of the woman requires treatment with ioxaglic acid.

The transient iodine overload following administration to the mother may result in foetal dysthyroidism if the examination takes place after 14 weeks of amenorrhoea.

Lactation
Ioxaglic acid is excreted in human milk and a risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued for 24 hours after administration of Hexabrix 320.

Effects on ability to drive and use machines
The effects on the ability to drive and to use machines have not been investigated.

Adverse reactions

In clinical trials done on 3791 patients, the reported adverse reactions were generally transient and mild or moderate in intensity. The most commonly reported adverse reactions were feeling of warmth and nausea.

Since post-marketing, the most commonly reported adverse reactions following administration of Hexabrix 320 are nausea, vomiting, urticaria, feeling of heat and pain at the administration site.

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

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.

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< 1/10), uncommon (> 1/1000 to 1< 1/100), rare (> 1/10,000 to 1<1/1000), very rare (< 1/10,000), not known (cannot be estimated from the available data). The data presented are from an observational study involving 4,995 patients.

<table>
<thead>
<tr>
<th>Organ Class System</th>
<th>Frequency: adverse reaction</th>
</tr>
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<tbody>
<tr>
<td>Immune system disorders</td>
<td>Unknown:</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity, anaphylactic reactions, anaphylactoid reactions</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Very rare:</td>
</tr>
<tr>
<td></td>
<td>Thyroid disorder</td>
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<tr>
<td>Classification</td>
<td>Description</td>
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<tr>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>* Very rare: Agitation*, confusional state*, hallucination</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>* Very rare: Headache, amnesia*, speech disorders*, tremor*, paraesthesia*, paresis*, convulsions*, somnolence*, coma*</td>
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<tr>
<td></td>
<td>Unknown: Syncopeº, presyncope</td>
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<tr>
<td><strong>Eye disorders</strong></td>
<td>* Very rare: Visual impairment*, photophobia, blindness transient</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>* Very rare: Hearing impaired*, vertigo</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>* Very rare: Arrhythmia, tachycardia, cardiac arrest, angina pectoris, myocardial infarction</td>
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<tr>
<td></td>
<td>Unknown: Venticular fibrillation, torsades de pointes</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>* Very rare: Circulatory collapse, thrombophlebitis, hypotension</td>
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<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>* Very rare: Sneezing, cough, throat tightness, dyspnoea, bronchospasm, laryngeal oedema, laryngospasm, pulmonary oedema, respiratory failure</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>* Very rare: Nausea, vomiting, abdominal pain, parotid gland enlargement, salivary hypersecretion, diarrhoea</td>
</tr>
</tbody>
</table>
| **Skin and subcutaneous tissue disorders**   | * Immediate: Pruritus, erythema, urticaria, angioedema  
|                                              | * Delayed: Eczema, maculo-papular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis |
| **Musculoskeletal and connective tissue disorders** | * Very rare: Joint effusion**, arthralgia**                                |
| **Renal and urinary disorders**              | * Very rare: Acute renal failure, anuria                                     |
| **Reproductive system and breast disorders** | * Very rare: Pelvic painº                                                   |
| **General disorders and administration site conditions** | * Very rare: Malaise, feeling hot, injection site pain, injection site extravasation, injection site inflammation, injection site necrosis |
|                                              | Unknown: Fever, chills, flushing, discomfort                                 |
| **Investigations**                           | * Very rare: Blood creatinin increased                                       |

* Examinations during which high levels iodinated contrast agent are present in cerebral arterial blood  
** Arthrography  
º Hysterosalpingography
Overdose

Overdose usually manifests as cardiorespiratory failure and renal insufficiency. Appropriate treatment must be directed at maintaining vital functions, quickly initiating symptomatic therapy. In the event of a very high dose, water and electrolyte loss can be compensated by suitably rehydration. Renal function must be monitored for at least three days. Haemodialysis may be carried out if necessary.

Pharmaceutical Precautions

Store below 25°C. Protect from light. Apart from Water for Injections and Dextrose Saline, Hexabrix 320 should not be mixed with any other substance. All presentations are intended as 'one dose' containers; none contain a bacteriostat.

Medicine Classification

General Sales Medicine.

Package Quantities

20 mL glass bottles: 25s
50 mL glass bottles: 25s
100 mL glass bottles: 10s

Further Information

Nil.

Name and Address

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