Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hexabrix 320 Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ioxaglic acid 53.33 % w/v
equivalent to 320 mg iodine per millilitre of solution.

Ioxaglic acid is present as meglumine ioxaglate and sodium ioxaglate.

(Sodium content:153 mEq/1)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to pale yellow solution with a pH of 6.5 to 7.6

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Low osmolar X-ray contrast medium for the opacification of the vascular system, urinary tract and joints and hysterosalpingography.

4.2 Posology and method of administration

Procedure	Product	Dosage and Administration
Femoral and other peripheral arteriographies	Hexabrix 320	15-20 ml. A similar or smaller dose is indicated for smaller arteries
Cerebral angiography (carotid and vertebral)	Hexabrix 320	Average adult dose: 6 - 8 ml for each injection. Up to 10 injections may be required.
Angiocardiography	Hexabrix 320	Multiple small test injections may be used for positioning catheter tip. *Adults*: 30-50 ml per injection Children and infants: 1-1, 5 ml per kg body weight. Multiple injections may be required, although total dosage should not normally exceed 4 ml per kg body weight.

Abdominal aortography (direct puncture or catheterization)	Hexabrix 320	*Adults:* 20-30 ml. Up to 50 ml may be used.
Thoracic aortography (including arch aortography)	Hexabrix 320	0.5 ml - 1.0 per body weight, up to 40 ml per injection. This may be repeated if necessary. Total dosage should not normally exceed 4 ml per kg body weight
Pulmonary angiography	Hexabrix 320	*Adults*: 20-40 ml. *Children*: 0.5-1 ml per kg body weight
Coronary arteriography	Hexabrix 320 to be diluted 50% with water for injection BP or sodium chloride and dextrose injection BP to produce a solution containing 160 mg of iodine per ml.	*Adults*: 3 to 8 ml injection depending on size of artery. Several injections may be necessary
Intravenous aortography	Hexabrix 320	*Adults and children*: 1-1.5 ml per kg body weight
Femoral venography and/or inferior vena cavography	Hexabrix 320	Adults: 25-50 ml
Leg phlebography	Hexabrix 320	20-50 ml injected into a vein in the foot.
Intravenous urography	Hexabrix 320	*Adults*: 20-80 ml; 60-100 ml may be used, provided the patient is not dehydrated. *Children*: under 12 kg - 2 ml per kg body weight; over 12 kg - 1.5 ml per body weight (with a minimum of 24 ml). Over 10 years of age: lower range of adult dose
Splenography portal venography	Hexabrix 320	Adults 20-40 ml by splenic puncture
Knee arthrography (double contrast)	Hexabrix 320	*Adults*: 4.5 together with injections of air before and after the positive contrast medium.
Hysterosalpingography	Hexabrix 320	10-20 ml are usually required Administrated by slow injection into uterine cervical canal via a syringe or suitable cannula.

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 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 should be administered with caution in well hydrated patients, and the administered dose should be reduced to the minimum.

4.3 Contraindications

- Hypersensitivity to ioxaglic acid or to any of the excipients (see section 6.1);
- History of major immediate or delayed cutaneous reaction (see section 4.8) to HEXABRIX injection;
- 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).

4.4 Special warnings and precautions for use

- An allergic risk exists, regardless of the route of administration and the dose.
- The risk of an allergic reaction associated with contrast agents administered locally for opacification of body cavities is not clear-cut:

a) Administration via certain specific routes (articular, biliary, intrauterine, etc.) results in varying degrees of systemic diffusion: systemic effects may be observed.
b) However, the immuno-allergic mechanism is not dose-dependent and immuno-allergic reactions can always occur, regardless of the route of administration.

General particulars corresponding to all iodinated contrast agents

Special warnings

Myelography is not an indication for Hexabrix.

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

All iodinated contrast media can cause minor or major reactions that can be life-threatening. These can occur immediately (within 60 minutes) or be delayed (within 7 days) and 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.

Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use especially in patients on beta blockers in whom adrenaline and vascular perfusion would be insufficiently effective.

Sufficient fluid intake (absence of dehydration) and normal electrolyte balance must be ensured in elderly patients, infants, small children, patients with renal damage (oliguria, polyuria) or hyperuricaemia, multiple myeloma, patients with plasmacytoma or diabetes mellitus particularly if it is long standing.

Several mechanisms have been evoked to explain the occurrence of these reactions:

- Direct toxicity on the vascular epithelium and tissue proteins.
- Pharmacological action that results in a modification in the concentration of certain endogenous factors (histamine, complement fractions, inflammation mediators), observed more frequently with hyperosmolar contrast media.
- IgE-mediated immediate allergic reaction to the contrast agent (anaphylaxis).
- Allergic reaction with cellular-type mechanism (delayed cutaneous reactions).

Patients who have already experienced a reaction after previous administration of an iodinated contrast agent present an increased risk of experiencing a further reaction following administration of the same or possibly another iodinated contrast agent, and are thus considered to be at-risk patients.

Iodinated contrast agents and the thyroid (see also Dysthyroidism)

Before the administration of iodinated contrast agents, it is important to ensure that the patient is not due to undergo a scintigraphic or biological examination of the thyroid or to receive radioactive iodine for therapeutic purposes.

Regardless of the route of administration, the administration of iodinated contrast agents disrupts hormone concentrations and the uptake of iodine by the thyroid or thyroid cancer metastases, until urine iodine levels have returned to normal.

Precautions for use
Intolerance to iodinated contrast agents:
Prior to the examination:

- Identify at-risk patients by a precise screening on their history.

Corticosteroids and antihistamines H1 have been proposed for pre-medication in patients presenting with the highest risk of reaction to contrast media (known intolerance to an iodinated contrast agent). These drugs do not, however, protect from the occurrence of severe or fatal anaphylactic shock.

During the procedure the following measures must be taken:
- Medical surveillance
- An indwelling intravenous catheter access.

After the procedure:

- After administration of the contrast agent, the patient must be monitored for at least 30 minutes since the majority of serious undesirable effects occur within this period of time.
- The patient must be informed about possible delayed reactions (up to 7 days after the examination) (see section 4.8 Undesirable effects).

Renal failure

Iodinated contrast agents can induce a transient alteration in renal function or worsen pre-existing renal failure. Preventive measures include:

- Identify at-risk patients, i.e. with dehydration, renal failure, diabetes, severe heart failure, monoclonal gammapathy (multiple myeloma, Waldenström's disease), hyperuricemia, a history of renal failure after iodinated contrast agent administration; infants below the age of one year and elderly subjects with atheroma.
- Hydrate when necessary using a saline solution.
- Avoid association of nephrotoxic drugs. If this cannot be avoided, reinforce monitoring of renal laboratory parameters. The drugs concerned include aminosides, organoplatinum compounds, high-dose methotrexate, pentamidine, foscarnet and certain antivirals (aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir), vancomycin, amphotericin B, immunosuppressants such as ciclosporin or tacrolimus, ifosfamide.
- Respect a time interval of at least 48 hours between two radiological examinations with injection of contrast agents or postpone any new examination until baseline renal function is restored.
- Prevent lactic acidosis in diabetic patients treated with metformin by monitoring serum creatinine levels. Normal renal function: treatment with metformin must be suspended before contrast agent injection and for at least 48 hours after or until normal renal function is restored. Impaired renal function: metformin is contra-indicated. In case of emergency: if the examination is mandatory, precautions must be taken: metformin discontinuation, hydration, monitoring of renal function and checking for signs of lactic acidosis.

Patients undergoing renal dialysis can receive iodinated contrast media since the latter are removed by dialysis.

However, prior advice from the dialysis unit should be taken.

Hepatic failure
Particular attention is necessary when a patient presents with both hepatic and renal failure since, in this situation, the risk for retention of the contrast agent is increased.

Asthma
Stabilisation of asthma is recommended before the injection of an iodinated contrast agent.
Due to an increased risk for bronchospasm, special caution should be taken in patients who have suffered an asthma attack within the 8 days preceding the examination.

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

Severe cardiovascular disease
In patients with early or patent heart failure, coronaropathy, pulmonary hypertension or valvulopathy, the risks of pulmonary oedema, myocardial ischaemia, rhythm disorders and severe haemodynamic disorders are increased after administration of the iodinated contrast agent.

Post-marketing cases of Torsade de Pointes have been reported in patients using sodium and meglumine ioxaglate, hence Hexabrix should be administered with caution to patients who have or may develop prolongation of QTc, including patients taking other medicinal products that lead to QT prolongation.

Central nervous system disorders
The benefit/risk ratio must be evaluated on a case-by-case basis:
- due to the risk of aggravation of neurological symptoms in patients with transient ischaemic stroke, acute cerebral infarct, recent intracranial haemorrhage, cerebral oedema, idiopathic or secondary (tumour, scar) epilepsy.
- in case of intra-arterial injection in alcoholic patients (acute or chronic alcoholism), and other drug-addicted subjects.

Pheochromocytoma
Patients with pheochromocytoma can develop a hypertensive crisis after intravascular administration of the contrast agent and must be monitored prior to the examination.

Myasthenia gravis
Administration of a contrast agent can worsen the symptoms of myasthenia gravis.

Exacerbation of side effects
Undesirable effects linked to iodinated contrast agent administration may be intensified in patients showing pronounced agitation, anxiety or pain. Appropriate management such as sedation may be necessary.

Other
This product contains 352 mg sodium per 100 ml.
This should be taken into account in patients on a strict low sodium diet.

Warnings and precautions for use specific to certain routes of administration with marked systemic diffusion
Medicinal products administered via the intrauterine route
Contraindication
Hysterosalpingography during pregnancy.

Precautions for use
Systematic screening for pregnancy should be carried out in women of child-bearing potential. Exposure of the female genital tract to X-rays should be carefully evaluated when weighing up the benefit/risk ratio.

In patients suffering from acute pelvic inflammation or infection, hysterosalpingography should only be performed after careful evaluation of the benefit/risk ratio.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products

- **Metformin in diabetic patients:** (see section 4.4 Precautions for use - renal failure).

- **Radiopharmaceuticals** (see section 4.4 Warnings)

  Iodinated contrast media alter for several weeks the uptake of radioactive iodine by the thyroid, which may on the one hand lead to impaired uptake in thyroid scintigraphy, and on the other hand to a decrease in the efficacy of Iodine 131 treatment. In patients due to undergo renal scintigraphy with injection of a radiopharmaceutical secreted by the renal tubule, it is preferable to carry out this examination before iodinated contrast agent injection.

- **Beta-blocking agents,** vasoactive substances, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists.

  These drugs reduce the efficacy of the cardiovascular compensation mechanism that occurs during haemodynamic disorders: the doctor must be informed before injection of the contrast agent and appropriate intensive care equipment must be available.

- **Diuretics**

  Due to the risk of dehydration caused by diuretics, hydroelectrolyte rehydration prior to the examination is necessary in order to minimize the risk of acute renal failure.

- **Interleukin-2**

  The risk of developing a reaction to the contrast agents is increased in the event of recent treatment with interleukin 2 (intravenous route): rash or, more rarely, hypotension, oliguria or even renal failure.

Other forms of interaction

High concentrations of iodinated contrast media in plasma and urine can interfere with the *in vitro* determination of bilirubin, proteins and inorganic substances (iron, copper, calcium and phosphate); it is recommended not to make these determinations within the first 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.

4.6 Fertility, pregnancy and lactation

Fertility

Toxicological studies on reproductive 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 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 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 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.

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

Organ Class System	**Frequency : adverse reaction**
Immune system disorders	Unknown: Hypersensitivity, anaphylactic reactions (including anaphylactic shock), anaphylactoid reactions
Endocrine disorders	Very rare: Thyroid disorder
Psychiatric disorders	Very rare: Agitation*, confusional state*, hallucination*
Nervous system disorders	Very rare: Headache, amnesia*, speech disorders*, tremor*, paraesthesia*, paresis*, convulsions*, somnolence*, coma* Unknown Syncope°, presyncope
Eye disorders	Very rare: Visual impairment*, photophobia, blindness transient
Ear and labyrinth disorders	Very rare: Hearing impaired*, vertigo
	Very rare: Arrhythmia, tachycardia, cardiac arrest, angina pectoris, myocardial infarction

Cardiac disorders	Unknown: ventricular fibrillation, torsade de pointes
Vascular disorders	Very rare: Circulatory collapse, thrombophlebitis, hypotension
Respiratory, thoracic and mediastinal disorders	Very rare: Sneezing, cough, throat tightness, dyspnoea, bronchospasm, laryngeal oedema, laryngospasm, pulmonary oedema, respiratory failure
Gastrointestinal disorders	Very rare: Nausea, vomiting, abdominal pain, parotid gland enlargement, salivary hypersecretion, diarrhoea
Skin and subcutaneous tissue disorders	Very rare: Immediate: Pruritus, erythema, urticaria, angioedema Delayed: Eczema, rash maculo-papular, Stevens-Johnson syndrome, toxic epidermal necrolysis Unknown: Dermatitis bullous
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 pain°
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, face oedema
Investigations	Very rare: Blood creatinin increased

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

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:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
E-mail: medsafety@hpra.ie.

4.9 Overdose

In laboratory animals the main signs of toxicity are convulsions, pulmonary congestion and oedema, respiratory depression, prostration, darkening of the eyes and hypersalivation; it is most unlikely that such toxic signs would occur in man, as it would be necessary to inject far greater doses than the minimum recommended. In man, overdosage as such should not arise but, since the causes of severe reactions to iodinate water-soluble contrast media are unknown, the information detailed under precautions and resuscitation should be carefully studied.
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 suitable rehydration. Renal function must be monitored for at least three days. Haemodialysis may be carried out if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Hexabrix procedures opacification of the vascular system and the urinary tract.

Pharmacological effects on the central nervous system, cardiovascular system and respiratory system are generally minor and of short duration.

No other pharmacological activity of note has been demonstrated.

5.2 Pharmacokinetic properties

Hexabrix 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.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Meglumine
Sodium calcium edentate
Sodium hydroxide
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

3 years.
Once opened, use immediately.

6.4 Special precautions for storage

Keep container in the outer carton.

6.5 Nature and contents of container

The Hexabrix 320 pack contains Type II clear colourless glass bottles with 20ml, 50ml and 100ml of solution for injection closed with an elastomer (chlorobutyl) stopper. The bottles are packed singly or in boxes containing 10 or 25 bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Guerbet
BP 57400
95943 Roissy CdG Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0686/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 May 1996

Date of last renewal: 09 May 2006

10 DATE OF REVISION OF THE TEXT

April 2015