Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Visipaque 320 mg I/ml Solution for Injection, polypropylene container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	Strength	Content pr. ml.
Iodixanol (INN)	270 mg I/ml	550 mg equiv. 270 mg I
Iodixanol (INN)	320 mg I/ml	652 mg equiv. 320 mg I

Iodixanol is a non-ionic, dimeric, hexaiodinated, water-soluble X-ray contrast medium. Pure aqueous solutions of iodixanol in all clinical relevant concentrations have a lower osmolality than whole blood and the corresponding strengths of the non-ionic monomeric contrast media. VISIPAQUE is made isotonic with normal body fluids by addition of electrolytes. The osmolality and viscosity values of VISIPAQUE are as follows:

Concentration	Osmolality * mOsm/kg H2O 37°C	Viscosity (mPa s)	
		20°C	37°C
270 mg I/ml	290	11.3	5.8
320 mg I/ml	290	25.4	11.4

* Method: Vapour - pressure osmometry.
The pH of the product is 6.8-7.6.
270 mg I/ml: This medicinal product contains 0.76 mg (0.03 mmol) sodium per ml. To be taken into consideration by patients on a controlled sodium diet.
320 mg I/ml: This medicinal product contains 0.45 mg (0.02 mmol) sodium per ml. To be taken into consideration by patients on a controlled sodium diet **(seesection4.4).**
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
VISIPAQUE is supplied ready to use as clear, colourless to pale yellow aqueous solutions.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
X-ray contrast medium for use in adults for cardioangiography, cerebral angiography (conventional), peripheral angiography, (conventional), urography, CT-enhancement and studies of the gastrointestinal tract, lumbar, thoracic and cervical myelography and for use in children for cardioangiography, urography, CT-enhancement and studies of the gastrointestinal tract.

4.2 Posology and method of administration

The dosage may vary depending on the type of examination, the age, weight, cardiac output and general condition of the patient and the technique used. Usually approximately the same iodine concentration and volume is used as with other iodinated X-ray contrast media in current use, but adequate diagnostic information has also been obtained in some studies with iodixanol injection with somewhat lower iodine concentration. Adequate hydration should be assured before and after administration as for other contrast media. The product is for intravenous, intra-arterial and intrathecal use, and for use in body cavities.

The following dosages may serve as a guide. The doses given for intra-arterial use are for single injections that may be repeated.

Indication/Investigation	Concentration	Volume

Intra-arterial use		
Arteriographies		
Selective cerebral	270/320[(1)] mg I/ml	5 - 10 ml per inj
Aortography	270/320 mg I/ml	40 - 60 ml per inj.
Peripheral	270/320 mg I/ml	30 - 60 ml per inj.
Selective visceral i.a. DSA	270 mg I/ml	10 - 40 ml per inj.
Cardioangiography		
Adults		
Left ventricle and aortic root inj.	320 mg I/ml	30 - 60 ml/inj.
Selective coronary arteriography	320 mg I/ml	4 - 8 ml/inj.
Children	270/320 mg I/ml	Depending on age, weight and pathology (recommended max total dose 10 ml/kg)

[(1)] Both strengths are documented, but 270 mg I/ml is recommended in most cases.

Indication/Investigation	Concentration	Volume
Intravenous use		
Urography		
Adults	270/320 mg I/ml	40 – 80 ml[(2)]
Children < 7 kg	270/320 mg I/ml	2 – 4 ml/kg
Children > 7 kg	270/320 mg I/ml	2 – 3 ml/kg
		All doses depending on age, weight and pathology (max. 50 ml).
Venography	270 mg I/ml	50 - 150 ml/leg
CT-enhancement		
Adults		
CT of the head	270/320 mg I/ml	50 – 150 ml
CT of the body	270/320 mg I/ml	75 – 150 ml
Children		
CT of the head and body	270/320 mg I/ml	2–3 ml/kg up to 50 ml (in a few cases up to 150 ml may be given)
Intrathecal use		
Lumbar and thoracic myelography (lumbar injection)	270 mg I/ml	10 – 12 ml[(3)]
	or 320 mg I/ml	10 ml[(3)]
Cervical myelography (cervical or lumbar injection)	270 mg I/ml	10 – 12 ml[(3)]
	or 320 mg I/ml	10 ml[(3)]

[(2)] In high-dose urography higher doses can be used.

[(3)] To minimize possible adverse reactions a total dose of 3.2 g iodine should not be exceeded.

Indication/Investigation	Concentration	Volume
Use in body cavities		The dosage must be adjusted individually to allow optimal visualisation
Arthrography	270 mg I/ml	1 – 15 ml
Hysterosalpingography (HSG)	270 mg I/ml	5 – 10 ml The recommended dose may be exceeded several times due to e.g. backflow into the vagina (up to 40 ml has been studied).
Gastrointestinal studies		
Oral use		
Adults		
Follow through	320 mg I/ml	80 – 200 ml has been studied
Oesophagus	320 mg I/ml	10 – 200 ml has been studied
Stomach	320 mg I/ml	20 – 200 ml has been studied
Children	270/320 mg I/ml	5 ml/kg b.w. 10-240 ml has been studied

Rectal use		
Children	270/320 mg I/ml	30 – 400 ml has been studied

For elderly patients, patients with hepatic and/or renal impairments, the usual/proposed doses for adults can be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Manifest thyrotoxicosis.

4.4 Special warnings and precautions for use

Special precautions foruse of non-ionic contrast media in general:
Hypersensitivity:
A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H1 and H2 antagonists might be considered in these cases.
The risk of serious reactions in connection with the use of VISIPAQUE is regarded as minor. However, iodinated contrast media may provoke anaphylactoid reactions or other manifestations of hypersensitivity.
The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/ anaphylactoid reactions should always be considered. The majority of serious undesirable reactions occur within the first 30 minutes. Late onset (that is 1 hour or more after application) hypersensitivity reactions can occur. A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment, should a serious reaction occur. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.
The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and reduces the responsiveness of treatment of anaphylactoid reactions with adrenaline.
Asthmatic patients are at higher risk on concomitant beta blocker therapy (see section 4.5) Patients should be observed for at least 30 minutes after administration of VISIPAQUE.
Coagulopathy:
Non-ionic, iodinated contrast media inhibit blood coagulation in vitro less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing contrast media including non-ionic media. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.
Risk for thromboembolism:
Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angio-cardiographic procedures with both ionic and non-ionic
contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended, including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing (e.g. with heparinised saline solutions), and minimizing the length of the procedure. Advanced life support facilities should be readily available.
Care should be taken in patients with homocystinuria. Hydration:
Adequate hydration should be assured before and after contrast media administration. This
applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction, as well as to infants, small children and elderly patients. Young infants (age < 1 year) and especially neonates are susceptible to electrolyte disturbance and haemodynamic alterations.
Cardio-circulatory reactions:
Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias. Rarely severe life-threatening reactions and fatalities of cardiovascular origin such as cardiac-, cardio- respiratory arrest and myocardial infarction have occurred.
CNS disturbances:
Encephalopathy has been reported with the use of iodixanol (see section 4.8). Contrast encephalopathy may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema within minutes to hours after administration of iodixanol, and generally resolves within days.
The product should be used with caution in patients with conditions that disrupt the integrity of the blood brain barrier (BBB), potentially leading to increased permeability of contrast media across the BBB and increasing the risk of encephalopathy.

Patients with acute cerebral pathology, tumours or a history of epilepsy are predisposed for seizures and merit particular care. Also, alcoholics and drug addicts have an increased risk for seizures and neurological reactions. In regard to intravascular application care should
be taken in patients with acute stroke or acute intracranial bleeding, in patients with altered blood brain barrier, cerebral oedema or acute demyelination.
If contrast encephalopathy is suspected, administration of iodixanol should be discontinued and appropriate medical management should be initiated.
Renal reactions:
A major risk factor for contrast medium-induced nephropathy is underlying renal dysfunction.
Diabetes mellitus and the volume of iodinated contrast medium administered are contributing factors in the presence of renal dysfunction. Additional concerns are dehydration, advanced arteriosclerosis, poor renal perfusion and the presence of other factors that may be nephrotoxic, such as certain medications or major surgery.
To prevent acute renal failure following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk. Patients with paraproteinemias (myelomatosis and Waldenström's macroglobulinemia) are also at risk.
Preventive measures include:
- Identification of high risk patients
- Ensuring adequate hydration. If necessary by maintaining an i.v. infusion from before the procedure until the contrast medium has been cleared by the kidneys.
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, or major surgery, until the contrast medium has been cleared.
- Dose reducing to a minimum.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

Iodinated contrast agents can be used by patients on haemodialysis as the agents are removed by the dialysis process.
Diabeticpatientsreceivingmetformin:
Intravascular contrast studies with iodinated contrast media can lead to acute alteration of renal function and have been associated with lactic acidosis in patients with impaired renal function receiving metformin.
To prevent lactic acidosis, serum creatinine levels should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium.
1. Patients with eGFR equal or greater than 60 ml/min/1.73 m2 (CKD 1 and 2) can continue to take metformin normally.
2. Patients with eGFR 30-59 ml/min/1.73 m2 (CKD 3):

a. Patients receiving intravenous contrast medium with eGFR equal or greater than 45 ml/min /1.73 m2 can continue to take metformin normally
b. In patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and
44 ml/min/1.73 m2 metformin should be discontinued 48 hours before
contrast medium and should only be restarted 48 hours after contrast medium if renal function has not deteriorated.

3. In patients with eGFR less than 30 ml/min/1.73 m2 (CKD 4 and 5) or with an intercurrent illness causing reduced liver function or hypoxia, metformin is contraindicated and iodinated contrast media should be avoided.
4. In emergency patients in whom renal function is either impaired or unknown, the physician shall weigh out risk and benefit of an examination with a contrast medium. Metformin should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

Impaired renal and hepatic function:
Particular care is required in patients with severe disturbance of both renal and hepatic function as they may have significantly delayed contrast medium clearance. Patients on haemodialysis may receive contrast media for radiological procedures. Correlation of the time of contrast media injection with the haemodialysis session is unnecessary because there is no evidence that haemodialysis protects patients with impaired renal function from contrast medium induced nephropathy.
Myasthenia gravis:
The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis.
Phaeochromocytoma:
In patients with phaeochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis.
Disturbances in thyroid function:
Patients with manifest but not yet diagnosed hyperthyroidism, patients with latent hyperthyroidism (e.g., nodular goitre) and patients with functional autonomy (often e.g. elderly patients, especially in regions with iodine deficiency) are at higher risk of acute thyrotoxicosis after use of iodinated contrast media. The additional risk should be evaluated in such patients before use of an iodinated contrast medium. Testing of thyroid function prior to contrast medium administration and/or preventative thyreostatic medication may be considered in patients with suspected hyperthyroidism. The patients at risk of should be monitored for the development of thyrotoxicosis in the weeks following the injection.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism.
Paediatric population:
Special attention should be paid to paediatric patients below 3 years of age because an incident underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. The incidence of hypothyroidism in patients younger than 3 years of age exposed to iodinated contrast media has been reported between 1.3% and 15% depending on the age of the subjects and the dose of the iodinated contrast agent and is more commonly observed in neonates and premature infants. Neonates may also be exposed through the mother during pregnancy.
Thyroid function should be evaluated in all paediatric patients younger than 3 years of age following exposure to iodinated contrast media. If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalised.
Extravasation:
VISIPAQUE due to its isotonicity gives rise to less local pain and extravascular oedema than hyperosmolar contrast media. In case of extravasation, elevating and cooling the affected site is recommended as routine measures. Surgical decompression may be necessary in cases of compartment syndrome.
VISIPAQUE may, dependent on the indication, contain more than 23 mg sodium per dose. This must be taken into consideration in patients on a controlled sodium diet.
Observation-time
After contrast medium administration, the patient should be observed for at least 30 minutes, since the majority of serious side effects occur within this time. However, experience shows that hypersensitivity reactions may appear up to several hours or days post injection.
Intrathecaluse
Following myelography the patient should rest with the head and thorax elevated by 20° for one hour. Thereafter he/she may ambulate carefully but bending down must be avoided. The head and thorax should be kept elevated for the first 6 hours if remaining in bed. Patients suspected of having a low seizure threshold should be observed during this period. Outpatients should not be completely alone for the first 24 hours.
Hysterosalpingography
Hysterosalpingography should not be performed during pregnancy or in the presence of acute pelvic inflammatory disease (PID).

4.5 Interaction with other medicinal products and other forms of interaction

All iodinated contrast media may affect the iodine binding capacity of the thyroid which may be reduced for up to several weeks, thus tests that measure iodine uptake (using radioactive iodine) will be affected.

High concentrations of contrast media in serum and urine can interfere with laboratory tests for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium and phosphate). These substances should therefore not be assayed on the day of examination.

Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking **metformin** (see section 4.4).

Patients treated with interleukin-2 less than two weeks prior to an iodinated contrast medium injection have an increased risk for delayed reactions (flu-like symptoms or skin reactions).

There is some evidence that use of beta blockers is a risk factor for anaphylactoid reactions to X-ray contrast media (severe hypotension has been seen with X-ray contrast media on beta blocker therapy).

Asthmatic patients are at higher risk on concomitant beta blocker therapy (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:
The safety of VISIPAQUE for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development. Since, wherever possible, radiation exposure should be avoided during pregnancy, the benefits of any X-ray examination, with or without contrast media, should be carefully weighed against

the possible risk. The product should not be used in pregnancy unless benefit outweighs risk and it is considered essential by the physician.

In neonates who have been exposed to iodinated contrast media in utero, it is recommended to monitor thyroid function (see section 4.4.).

Breast-feeding:
Contrast media are poorly excreted in human breast milk and minimal amounts are absorbed by the intestine. Breast feeding may be continued normally when iodinated contrast media are given to the mother.

Fertility:
The effect of VISIPAQUE on human reproduction has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive or use machines have been performed however, it is not advisable to drive a car or use machines during the first 24 hours following intrathecal examination.

4.8 Undesirable effects

Below are listed possible side effects in relation with radiographic procedures which include the use of Visipaque.
Undesirable effects associated with VISIPAQUE are usually mild to moderate and transient in nature. Serious reactions as well as fatalities are only seen on very rare occasions, these may include acute-on-chronic renal failure, acute renal failure, anaphylactic or anaphylactoid shock, hypersensitivity reaction followed by cardiac reactions (Kounis' syndrome), cardiac or cardio-respiratory arrest and myocardial infarction. Cardiac reaction may be promoted by the underlying disease or the procedure.
Hypersensitivity reactions may present as respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus, severe skin reactions, angioneurotic oedema, hypotension, fever, laryngeal oedema, bronchospasm or pulmonary oedema. In patients with autoimmune diseases cases of vasculitis and SJS-like syndrome were observed.
They may appear either immediately after the injection or up to a few days later.
Hypersensitivity reactions may occur irrespectively of the dose and mode of administration and mild symptoms may represent the first signs of a serious anaphylactoid reaction/shock.
Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the vascular access. Patients using beta blockers may present with atypical symptoms of hypersensitivity which may be misinterpreted as a vagal reaction.
A minor transient increase in serum creatinine is common after iodinated contrast media, but is usually of no clinical relevance.
The frequencies of undesirable effects are defined as follows:
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) and not known (cannot be estimated from the available data).
The listed frequencies are based on internal clinical documentation and published studies, comprising more than 57,705 patients.
Intravascular administration:
Blood and lymphatic system disorders
Not known: Thrombocytopenia
Immune system disorders:
Uncommon: Hypersensitivity
Not known: Anaphylactic/anaphylactoid shock, anaphylactic/anaphylactoid reaction including life-threatening or fatal anaphylaxis
Endocrine disorders:
Not known: Hyperthyroidism, hypothyroidism
Psychiatric disorders:
Very rare: Agitation, anxiety
Not known: Confusional state
Nervous system disorders:
Uncommon: Headache
Rare: Dizziness, sensory abnormalities including dysgeusia, paraesthesia, parosmia
Very rare: Cerebrovascular accident,amnesia, syncope, tremor (transient), hypoaesthesia

Not known: Coma, disturbance in consciousness, convulsion, transient contrast-induced encephalopathy * caused by extravasation of contrast media, which can manifest as sensory, motor or global neurological dysfunction
* See Description of selected adverse reactions for more details.
Eye disorders:
Very rare: Cortical blindness (transient), visual impairment (including diplopia, blurred vision), eyelid oedema
Cardiac disorders:
Rare: Arrhythmia (including bradycardia, tachycardia), myocardial infarction
Very rare: Cardiac arrest, palpitations
Not known: Cardiac failure, ventricular hypokinesia, spasms of coronary arteries, cardio-respiratory arrest, conduction abnormalities, coronary artery thrombosis, angina pectoris
Vascular disorders:
Uncommon: Flushing
Rare: Hypotension
Very rare: Hypertension, ischaemia
Not known: Shock, arterial spasm, thrombosis, thrombophlebitis
Respiratory, thoracic and mediastinal disorders:
Rare: Cough, sneezing
Very rare: Dyspnoea, throat irritation, laryngeal oedema
Not known: Non-cardiogenic pulmonary oedema, respiratory arrest, respiratory failure, bronchospasm, throat tightness, pharyngeal oedema
Gastrointestinal disorders:
Uncommon: Nausea, vomiting
Very rare: Abdominal pain/discomfort, diarrhoea
Not known: Acute pancreatitis, pancreatitis aggravated, salivary gland enlargement
Skin and subcutaneous system disorders
Uncommon: Rash or drug eruption, pruritus, urticaria
Very rare: Angioedema, erythema, hyperhidrosis
Not known: Bullous or exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders:
Very rare: Back pain, muscle spasm
Not known: Arthralgia
Renal and urinary disorders:
Uncommon: Acute kidney injury or nephropathy toxic (contrast induced nephropathy-CIN)
Not known: Increased blood creatinine
General disorders and administration site conditions:
Uncommon: chest pain, feeling of body temperature change
Rare: Shivering (chills), pyrexia, pain and discomfort, administration site reactions including extravasation
Very rare: Asthenic conditions (e.g. malaise, fatigue), face oedema, localised oedema
Not known: Swelling
Injury, poisoning and procedural complications:
Not known: Iodism

Intrathecal administration:

Undesirable effects following intrathecal use may be delayed and present some hours or even days after the procedure. The frequency is similar to lumbar puncture alone.
Meningeal irritation giving photophobia and meningism and frank chemical meningitis have been observed with other non-ionic contrast media. The possibility of infective meningitis should also be considered.
Immune system disorders:
Not known: Hypersensitivity, including anaphylactic/ anaphylactoid reactions
Nervous system disorders:
Uncommon: Headache (may be severe and lasting)
Not known: Coma, disturbance in consciousness, convulsion, transient contrast-induced encephalopathy * caused by extravasation of contrast media, which can manifest as sensory, motor or global neurological dysfunction
Gastrointestinal disorders:
Uncommon: Vomiting
Not known: Nausea
Musculoskeletal and connective tissue disorders:
Not known: Muscle spasm
General disorders and administration site conditions:
Not known: Shivering, pain at injection site

Hysterosalpingography (HSG):
Immune system disorders:
Not known: Hypersensitivity
Nervous system disorders:
Common: Headache
Gastrointestinal disorders:
Very common: Abdominal pain
Common: Nausea
Uncommon: Vomiting
Reproductive system and breast disorders:
Very common: Vaginal haemorrhage
General disorders and administration site conditions:
Common: Pyrexia
Not known: Shivering, injection site reaction
Arthrography:
Immune system disorders:
Not known: Hypersensitivity, including anaphylactic/ anaphylactoid reactions.
General disorders and administration site conditions:
Common: Injection site pain
Not known: Shivering
Examination of the GI tract:
Immune system disorders:
Not known: Hypersensitivity, including anaphylactic/ anaphylactoid reactions.
Gastrointestinal disorders:
Common: Diarrhoea, abdominal pain, nausea
Uncommon: Vomiting
General disorders and administration site reaction
Not known: Shivering
Description of selected adverse reactions:
Transient contrast-induced encephalopathy:
In unknown occasions the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex that may cause contrast-induced encephalopathy. The symptoms may include agitation,transient cortical blindness, amnesia, hallucination, paralysis, paresis, disorientation, transient speech disorder, aphasia, dysarthria.
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 to
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

Overdosage is unlikely in patients with a normal renal function. The duration of the procedure is important for the renal tolerability of high doses of contrast media ($t_{½}$ ~ 2 hours). In the event of accidental overdosing, the water and electrolyte losses must be compensated by infusion. Renal function should be monitored for at least the next 3 days. If needed, haemodialysis may be used to remove iodixanol from the patient's system. There is no specific antidote. Treatment of overdose is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: X-ray contrast medium, iodinated

ATC: V08A B09

The organically bound iodine absorbs radiation in the blood vessels/tissues when it is injected.

For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iodixanol in healthy volunteers, no significant deviation from preinjection values has been found. The few changes observed in the laboratory parameters were minor and considered to be of no clinical importance.

VISIPAQUE induces only minor effects on renal function in patients. In 64 diabetic patients with serum creatinine levels of 1.3-3.5 mg/dl, VISIPAQUE use resulted in 3% of patients experiencing a rise in creatinine of ≥ 0.5 mg/dl and 0% of patients with a rise of ≥ 1.0 mg/dl. The release of enzymes (alkaline phosphatase and N-acetyl-ß-glucosaminidase) from the proximal tubular cells is less than after injections of non-ionic monomeric contrast media and the same trend is seen compared to ionic dimeric contrast media. VISIPAQUE is also well tolerated by the kidney.

Cardiovascular parameters such as LVEDP, LVSP, heart rate and QT-time as well as femoral blood flow were less influenced after VISIPAQUE than after other contrast media, where measured.

5.2 Pharmacokinetic properties

Iodixanol is rapidly distributed in the body with a mean distribution half-life of approximately 21 minutes. The apparent volume of distribution is of the same magnitude as the extracellular fluid (0.26 l/kg b.w.), indicating that iodixanol is distributed in the extra-cellular volume only. No metabolites have been detected. The protein binding is less than 2%.

The mean elimination half-life is approximately 2 hours. Iodixanol is excreted mainly through the kidneys by glomerular filtration. Approximately 80% of the administered dose is recovered unmetabolized in the urine within 4 hours and 97% within 24 hours after intravenous injection in healthy volunteers. Only about 1.2% of the injected dose is excreted in faeces within 72 hours. The maximum urinary concentration appears within approximately 1 hour after injection.

No dose dependent kinetics have been observed in the recommended dose range.

No specific pharmacokinetic studies have been performed for use in body cavities.

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, and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium chloride
Calcium chloride dihydrate
Sodium calcium edetate
Hydrochloric acid (pH adjustment)
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. A separate syringe should be used.

6.3 Shelf life

3 years.
The product must be used immediately after opening.

6.4 Special precautions for storage

Glasscontainers:
Do not store above 30 C, keep the container in the outer carton. Protect from secondary X- rays. The product can be stored for 1 month at 37 C.
PolypropyleneBottles:
Do not store above 30°C. Keep the container in the outer carton. Protect from secondary
X-rays. The product in 50, 100, 200 and 500 ml polypropylene bottles can be stored for up to 1 month at 37°C.

6.5 Nature and contents of container

Glasscontainers:
The product is filled in injection vials (20 ml) and infusion bottles (50, 100, 200 and 500 ml). The glass vials/bottles are made of colourless highly resistant borosilicate glass (Ph. Eur. Type I), closed with halobutyl rubber stoppers (Ph. Eur. Type I), and sealed with complete tear off caps with coloured plastic "flip-off" tops.
Polypropylenebottles:
The product is filled in polypropylene bottles.
Bottles of 50, 100, 200 and 500 ml are closed with halobutyl rubber stoppers (Ph. Eur. Type I), and supplied with a plastic screw cap which is provided with a tamper proof ring.
Glasscontainers:
The product is supplied as:
270 mg I/ml and 320 mg I/ml:

Vial/Bottle size	Pack size/Fill volume
20 ml	10 vials of 20 ml
50 ml	10 bottles of 50 ml
100 ml	1 bottle of 100 ml, 10 bottles of 100 ml
200 ml	1 bottle of 200 ml, 6 bottles of 200 ml
500 ml	1 bottle of 500 ml, 6 bottles of 500 ml

PolypropyleneContainers:
The product is supplied as:
270 mg I/ml and 320 mg I/ml:
Bottles with rubber stopper and plastic screw cap:

Bottle size	Pack size/Fill volume
50 ml	1 bottle of 50 ml, 10 bottles of 50 ml
100 ml	1 bottle of 75 ml, 10 bottles of 75 ml 1 bottle of 100 ml, 10 bottles of 100 ml
200 ml	1 bottle of 150 ml, 10 bottles of 150 ml 1 bottle of 175 ml, 10 bottles of 175 ml 1 bottle of 200 ml, 10 bottles of 200 ml
500 ml	1 bottle of 500 ml, 6 bottles of 500 ml

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

For single use only. Discard any unused contents.

Like all parenteral products, VISIPAQUE should be inspected visually for particulate matter, discolouration and the integrity of the container prior to use.

The product should be drawn into the syringe immediately before use. VISIPAQUE may be warmed to body temperature before administration.

Additional instructions for auto injector/pump
The 500 ml contrast medium bottles should only be used in connection with auto injectors/pumps approved for this volume. A single piercing procedure should be used.

The line running from the auto injector/pump to the patient must be exchanged after each patient. Any unused portions of the contrast medium remaining in the bottle and all connecting tubes must be discarded at the end of the day. When convenient, smaller bottles can also be used. Instructions from the manufacturer of the auto injector/pump must be followed.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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