

## New Zealand Datasheet

### Name of Medicine

VISIPAQUE™

Iodixanol Injection 150 mg l/ml, 270 mg l/ml, 320 mg l/ml

### Presentation

VISIPAQUE injectable solution is provided as a ready-to-use sterile, pyrogen-free, colourless to pale yellow solution, in concentrations of 150, 270 and 320 mg of organically bound iodine per ml (305, 550 and 652 mg of iodixanol per ml, respectively). All solutions of iodixanol are hypotonic to blood. Sodium chloride and calcium chloride have been added resulting in an isotonic solution for injection. VISIPAQUE (150 mg l/ml) contains 0.09 mg calcium chloride dihydrate per ml and 4.03 mg sodium chloride per ml, VISIPAQUE (270 mg l/ml) contains 0.07 mg calcium chloride dihydrate per ml and 1.87 mg sodium chloride per ml, and VISIPAQUE (320 mg l/ml) contains 0.04 mg calcium chloride dihydrate per ml and 1.10 mg sodium chloride per ml providing for both concentrations a sodium/calcium ratio equivalent to blood. In addition, each millilitre contains 1.2 mg trometamol and 0.1 mg sodium calcium edetate; the pH is adjusted between 6.8 and 7.7 with hydrochloric acid and/or sodium hydroxide at 22°C. All solutions are terminally sterilised by autoclaving and contain no preservatives.

### Uses

#### Actions

VISIPAQUE is a dimeric, non-ionic, water-soluble, radiographic contrast medium with a molecular weight of 1550.20 (iodine content 49.1%). 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 laboratory parameters were minor and considered to be of no clinical importance.

VISIPAQUE induces only minor effects on renal function in patients. In 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% with a rise of = 1.0 mg/dl. The release of enzymes (alkaline phosphatase and N-acetyl- $\beta$ -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.

#### Pharmacokinetics

Following intravascular injection, VISIPAQUE is distributed in the extracellular fluid and is excreted unchanged by glomerular filtration. It will opacify those vessels in the path of flow of the contrast medium, permitting radiographic visualisation of the internal structures until significant dilution and elimination occur. The degree of density enhancement is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid intravascular injection.

Plasma and urine levels indicate that body clearance of iodixanol is due primarily to renal clearance. Approximately 97% of the injected dose of VISIPAQUE is excreted unchanged in urine within 24 hours, with less than 2% excreted in faeces within five days post-injection.

The following mean pharmacokinetic values were observed in a single-dose Phase 1 study following the intravenous administration of VISIPAQUE (0.3 to 1.2 g I/kg body weight) to 40 healthy adult male human subjects: distribution half-life ( $t_{1/2\alpha}$  = 21 min) elimination half-life ( $t_{1/2\beta}$  = 123 min) volume of distribution ( $V_D$  = 0.26 l/kg bodyweight) and renal clearance ( $Cl$  = 110 ml/min). These values were independent of the dose levels administered.

Pharmacokinetics have not been studied in patients with renal impairment, however, prolonged plasma levels of VISIPAQUE and other iodinated contrast agents, may be anticipated in patients with renal impairment due to decreased renal elimination.

VISIPAQUE displayed no protein binding *in vitro* (less than 2% detectable limit) at a 1.2 mg I/ml concentration in human plasma. No significant metabolism, deiodination or biotransformation has been detected in animals.

VISIPAQUE probably crosses the placental barrier in humans by simple diffusion. It is not known to what extent VISIPAQUE is excreted in human milk; studies with other contrast agents show they are excreted unchanged in the milk. Animal studies indicate that VISIPAQUE may not cross an intact blood-brain barrier to any significant extent following intravascular administration.

### **Indications**

VISIPAQUE is indicated for cardioangiography, cerebral angiography (conventional and i.a.DSA), peripheral arteriography (conventional and i.a.DSA), abdominal angiography (i.a.DSA), urography, venography, CT-enhancement. Lumbar, thoracic and cervical myelography.

### **Dosage and 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.

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
<b><u>Intra-arterial use</u></b>		
<b>Arteriographies</b>		
selective cerebral	270/320 <sup>(1)</sup> mg/ml	5-10 ml per inj.
selective cerebral i.a.DSA	150 mg l/ml	5-10 ml per inj.
aortography	270/320 mg l/ml	40-60 ml per inj.
peripheral	270/320 mg l/ml	30-60 ml per inj.
peripheral i.a.DSA	150 mg l/ml	30-60 ml per inj.
selective visceral i.a.DSA	270 mg l/ml	10-40 ml per inj.
<b>Cardioangiography, <u>Adults</u></b>		
Left ventricle and aortic root inj.,	320 mg l/ml	30-60 ml per inj.
Selective coronary arteriography	320 mg l/ml	4-8 ml per inj.
<u>Children</u>	270/320 mg l/ml	Depending on age, weight and pathology (recommended max total dose 10 ml/kg).
<b><u>Intravenous use</u></b>		
<b>Urography,</b>		
<u>Adults</u>	270/320 mg/ml	40-80 ml <sup>(2)</sup>
<u>Children</u> < 7 kg	270/320 mg l/ml	2-4 ml/kg
<u>Children</u> > 7 kg	270/320 mg l/ml	2-3 ml/kg
		All doses depending on age, weight and pathology (max.50ml).
<b>Venography</b>	270 mg l/ml	50-150 ml/leg
<b>CT-enhancement</b>		
CT of the head, <u>adults</u>	270/320 mg l/ml	50-150 ml
CT of the body, <u>adults</u>	270/320 mg l/ml	75-150 ml
<u>Children</u> , CT of the head and body	270/320 mg l/ml	2-3 ml/kg up to 50 ml (in a few cases up to 150 ml may be given)
<b><u>Intrathecal use</u></b>		
<b>Lumbar and thoracic myelography</b> (lumbar injection)		
	270 mg l/ml or 320 mg l/ml	10-12 ml <sup>(3)</sup>
<b>Cervical myelography</b> (cervical or lumbar injection)		
	270 mg l/ml or 320 mg l/ml	10 ml <sup>(3)</sup>
		10-12 ml <sup>(3)</sup>
		10 ml <sup>(3)</sup>

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

(2) 80 ml may be exceeded in selected cases.

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

## Elderly

As for other adults.

## Contraindications

Manifest thyrotoxicosis. History of serious hypersensitivity reaction to VISIPAQUE.

## Warnings and Precautions

### Special precautions for use of non-ionic contrast media in general:

A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H<sub>1</sub> and H<sub>2</sub> antagonists might be considered in these cases.

The risk of serious reactions in connection with use of VISIPAQUE is regarded as minor. However, iodinated contrast media may provoke anaphylactoid reactions or other manifestations of hypersensitivity. 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.

Non-ionic contrast media have less effect on the coagulation system *in vitro*, compared to ionic contrast media. When performing vascular catheterization procedures one should pay meticulous attention to the angiographic technique and flush the catheter frequently (e.g.: with heparinised saline) so as to minimise the risk of procedure-related thrombosis and embolism.

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.

Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias.

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.

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.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

To prevent lactic acidosis, serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium. Normal serum creatinine / renal function: Administration of metformin should be stopped at the time of administration of contrast medium and not resumed for 48 hours or until renal function / serum creatinine is normal. Abnormal serum creatinine / renal function: Metformin should be stopped and the contrast medium examination delayed for 48 hours. Metformin should only be restarted if renal function / serum creatinine is unchanged. In emergency cases where renal function is abnormal or unknown, the physician should evaluate the risk / benefit of the contrast medium examination, and precautions should be implemented: Metformin should be stopped, patient hydrated, renal function monitored and patient observed for symptoms of lactic acidosis.

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.

The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis. In patients with pheochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis. Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goitre may be at risk of developing hyperthyroidism following injection of iodinated contrast media. One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media.

Extravasation of VISIPAQUE has not been reported, but it is likely that 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.

#### Observation-time:

After contrast medium administration the patient should be observed for at least 30 minutes, since the majority of serious side effects occurs within this time. However, experience shows that hypersensitivity reactions may appear up to several hours or days post injection.

#### **Intrathecal use**

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.

#### **Use in 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.

### **Use in Lactation**

Breast feeding may be continued normally when iodinated contrast media are given to the mother.

### **Effects on Ability to Drive and Use Machines**

It is not advisable to drive a car or use machines during the first 24 hours following intrathecal examination.

### **Adverse Effects**

Below are listed possible side effects in relation with radiographic procedures which include the use of VISIPAQUE.

#### **Intravascular use**

Undesirable effects associated with the use of iodinated contrast media are usually mild to moderate and transient in nature, and less frequent with non-ionic than with ionic contrast media. Serious reactions as well as fatalities are only seen on very rare occasions.

The most frequent adverse event is a mild, general feeling of warmth or cold. Heat sensation in peripheral angiography is common (Incidence: >1:10), while distal pain occurs occasionally (Incidence < 1:10, but >1:100).

Abdominal discomfort/pain is very rare (Incidence < 1:1000) and gastrointestinal reactions like nausea or vomiting are rare (Incidence < 1:100, but > 1:1000).

Hypersensitivity reactions occur occasionally and usually present as mild respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus and angioedema. They may appear either immediately after the injection or up to a few days later. Hypotension or fever may occur. Severe till toxic skin reactions have been reported. Severe manifestations such as laryngeal oedema, bronchospasm, pulmonary oedema and anaphylactic shock are very rare.

Anaphylactoid reactions may occur irrespectively of the dose and mode of administration and mild symptoms of hypersensitivity may represent the first signs of a serious reaction. 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 anaphylaxis which may be misinterpreted as a vagal reaction.

Vagal reactions giving hypotension and bradycardia are seen on very rare occasions.

Iodism or "iodide mumps" is a very rare complication of iodinated contrast media resulting in swelling and tenderness of the salivary glands for up to approximately 10 days after the examination.

A minor transient increase in S-creatinine is common after iodinated contrast media, but usually of no clinical relevance. Renal failure is very rare. However, fatalities have been reported in high risk patient groups.

Arterial spasm may follow injection into coronary, cerebral or renal arteries and result in transient ischaemia.

Neurological reactions are very rare. They may include headache, dizziness, seizures or transient motor or sensory disturbances. On very rare occasions the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex being visible on CT-scanning until the day following examination, sometimes associated with transient confusion or cortical blindness.

Cardiac complications are very rare, including arrhythmias, depression or signs of ischaemia. Hypertension may occur.

Post phlebographic thrombophlebitis or thrombosis is very rare. A very few cases of arthralgia have been reported.

Severe respiratory symptoms and signs (including dyspnoea and non-cardiogenic pulmonary oedema), and cough may occur.

### **Intrathecal use**

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.

Headache, nausea, vomiting or dizziness are common and may largely be attributed to pressure loss in the subarachnoid space resulting from leakage at the puncture site. Some of these patients may experience a severe headache lasting for several days. Excessive removal of cerebrospinal fluid should be avoided in order to minimise pressure loss.

Mild local pain and radicular pain at the site of injection may occur.

Meningeal irritation giving photophobia and meningism and frank chemical meningitis have been observed with other non-ionic iodinated contrast media. The possibility of an infective meningitis should also be considered.

Similarly, manifestations of transient cerebral dysfunction have been seen on very rare occasions with other non-ionic iodinated contrast media. These include seizures, transient confusion or transient motor or sensory dysfunction. Changes in the EEG was noted in a few of these patients.

### **Interactions**

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 Warnings and Precautions).

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

### **Laboratory Tests**

All iodinated contrast media may interfere with tests on thyroid function, thus the iodine binding capacity of the thyroid may be reduced for up to several weeks.

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.

## Overdosage

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 ( $t_{1/2} \sim 2$  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.

## Pharmaceutical Precautions

Protect vials, bottles and flexible containers of VISIPAQUE from strong daylight and direct exposure to sunlight. Store at controlled room temperature, 15°C to 30°C. Do not remove foil overwrap, which serves as a moisture and light barrier, from flexible containers until ready to use. VISIPAQUE in glass containers and in polypropylene bottles 50 ml and over in size may be stored at 37°C for up to one month prior to use. 10 ml and 20 ml polypropylene bottles may be stored at 37°C for up to one week prior to use.

Do not freeze. Freezing may compromise the closure integrity of these packages. Do not use if the product is inadvertently frozen.

## Medicine Classification

General Sale Medicine

## Package Quantities

VISIPAQUE (iodixanol) injection 150 mg l/ml:

50 ml glass vial, boxes of 10

200 ml glass bottle, boxes of 6

500 ml glass bottle, boxes of 6

VISIPAQUE (iodixanol) injection 270 mg l/ml:

20 ml glass vial, boxes of 10

50 ml glass or polypropylene bottles, boxes of 10

75 ml polypropylene bottles, boxes of 10

100 ml glass or polypropylene bottles, boxes of 10

150 ml polypropylene bottles, boxes of 10

200 ml glass or polypropylene bottles, boxes of 6 or 10

500 ml glass or polypropylene bottles, boxes of 6

VISIPAQUE (iodixanol) injection 320 mg l/ml:

20 ml glass vial, boxes of 10

50 ml glass or polypropylene bottles, boxes of 10

75 ml polypropylene bottles, boxes of 10

100 ml glass or polypropylene bottles, boxes of 10

150 ml polypropylene bottles, boxes of 10

200 ml glass or polypropylene bottles, boxes of 6 or 10

500 ml glass or polypropylene bottles, boxes of 6

Not all presentations are marketed.

## Further Information

### Incompatibilities

No incompatibility has been found. However, VISIPAQUE should not be directly mixed with other drugs. A separate syringe should be used.

## Instructions for Use/Handling

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. Vials are intended for single use only, any unused portions must be discarded.

VISIPAQUE may be warmed to body temperature (37°C) before administration.

### Additional instruction 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.

### Physical Properties of Visipaque

The three concentrations of VISIPAQUE, 150 mg l/ml, 270 mg l/ml and 320 mg l/ml have the following physical properties:

Parameter	Concentration (mg l/ml)		
	150	270	320
Osmolality (mOsm/kg water) (vapour pressure at 37°C)	290	290	290
Viscosity (cp) at 20°C	2.7	12.7	26.6
at 37°C	1.7	6.3	11.8

### Trademarks

VISIPAQUE is a trademark of GE Healthcare.

GE and the GE monogram are trademarks of General Electric Company.

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