New Zealand Datasheet

1 PRODUCT NAME
VISIPAQUE™

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Iodixanol Injection 270 mg I/ml, 320 mg I/ml

3 PHARMACEUTICAL FORM
VISIPAQUE injectable solution is provided as a ready-to-use sterile, pyrogen-free, colourless to pale yellow solution, in concentrations of 270 and 320 mg of organically bound iodine per ml (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 (270 mg I/ml) contains 0.07 mg calcium chloride dihydrate per ml and 1.87 mg sodium chloride per ml, and VISIPAQUE (320 mg I/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 22ºC. All solutions are terminally sterilised by autoclaving and contain no preservatives.

Physical Properties of VISIPAQUE
The two concentrations of VISIPAQUE, 270 mg I/ml and 320 mg I/ml have the following physical properties:

Parameter	Concentration (mg I/ml)	
	270	320
Osmolality (mOsm/kg water) (vapour pressure at 37ºC)	290	290
Viscosity (mPa-s) at 20ºC at 37ºC	11.3 5.8	25.4 11.4
Density (g/ml) at 20°C	1.369	1.356
At 37°C	1.314	1.303

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
This medicinal product is for diagnostic use only.

VISIPAQUE is indicated, in adult patients, for angiocardiography, peripheral arteriography, visceral arteriography, cerebral arteriography, contrast-enhanced computed tomography of the head and body, excretory urography and venography. In arteriography, VISIPAQUE may be used for both conventional radiography and digital subtraction angiography (DSA).

In children, VISIPAQUE is indicated for cardioangiography, urography, CT-enhancement and studies of the upper gastrointestinal tract.

4.2 Dose and method of administration
Diagnostic procedures that involve the use of radiopaque imaging agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed.

Preparation of the patient will vary with the particular agent used, preference of the radiologist and the type of radiologic procedure performed. Specific radiographic procedures used will depend on the state of the patient and the diagnostic indications.

The combination of volume and concentration of VISIPAQUE to be used should be carefully individualised, accounting for factors such as age, body weight, size of the vessel, rate of blood flow within the vessel, cardiac output, indication for examination, and timing of the X-ray or CT scan. Other factors to be considered are anticipated pathology, degree and extent of opacification required, structure or area to be examined, disease processes affecting the patient, and equipment and 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.

Generally recommended doses are contained in the following tables. The doses given for intra-arterial use are for single injections that may be repeated:

Adult Dosages

Indication/Investigation	**Concentration**	**Volume**
Intra-arterial use		
Arteriographies		
selective cerebral	270/320[1] mgI/ml*	5-10 ml per inj.[2]
aortography	270/320 mgI/ml	40-60 ml per inj.[3]
peripheral	270/320 mgI/ml	30-60 ml per inj.[3]
selective visceral i.a.DSA	270 mgI/ml	10-40 ml per inj.[3]
Cardioangiography		
Left ventricle and aortic root inj.,	320 mg I/ml	30-60 ml per inj.[4]
Selective coronary arteriography	320 mg I/ml	4-8 ml per inj.[4]
Intravenous use		
Urography	270/320 mgI/ml	40-80 ml[5]
Venography	270 mgI/ml	50-150 ml/leg
CT-enhancement		
CT of the head	270/320 mgI/ml	50-150 ml
CT of the body	270/320 mgI/ml	75-150 ml

Paediatric Dosages

Intra-arterial use		
Cardioangiography	320 mgI/ml*	1-2 ml/kg with max recommended dose of 10 ml/kg. All doses depending on age, weight and pathology.
Intravenous use		
Urography**		
Children < 7 kg	270/320 mgI/ml	2-4 ml/kg
Children > 7 kg	270/320 mgI/ml	2-3 ml/kg All doses depending on age, weight and pathology (max.50ml).
CT-enhancement		
CT of the head and body	270/320 mgI/ml	2-3 ml/kg up to 50 ml (in a few cases up to 150 ml may be given)
Upper Gastrointestinal Studies		
Children	270/320 mgI/ml	The dosage must be adjusted individually to allow optimal visualisation 5 ml/kg b.w.*** 10-240 ml has been studied

(1) Both strengths are documented, but 270 mg I/ml is recommended in most cases.
(2) Total dose for combined procedures should not exceed 0.8 g I/kg body weight.
(3) Total dose for combined procedures should not exceed 1.2 g I/kg body weight.
(4) Total dose for combined procedures should not exceed 0.9 g I/kg body weight.
(5) 80 ml may be exceeded in selected cases. Total dose for combined procedures should not exceed 0.46 g I/kg body weight.
* mg I/ml means milligrams of Iodine per millilitre
** Infants less than 2500 gm were excluded from urography studies.
*** b.w. means body weight

Elderly
As for other adults.

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

4.3 Contraindications

Hypersensitivity to the active substance or iodine or hypersensitivity to any of the excipients.

Manifest thyrotoxicosis.

History of serious hypersensitivity reaction to VISIPAQUE.

4.4 Special warnings and precautions for use

Precautions for use of non-ionic contrast media in general:
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.

The use of beta-adrenergic blocking agents may lower the threshold for bronchospasm in asthmatic patients after contrast medium administration and reduce the responsiveness of treatment with adrenaline.

As with other iodinated contrast agents, the use of VISIPAQUE injection contrast enhancement may obscure some lesions which are seen on previously unenhanced CT scans.

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. If contrast encephalopathy is suspected, administration of iodixanol should be discontinued and appropriate medical management should be initiated.

Enhancement of the inferior vermis following contrast agent administration has resulted in false-positive diagnosis.

Hydration
Patients should be well hydrated prior to, and following, administration of any contrast medium, including VISIPAQUE, in order to prevent from acute renal failure. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction and elderly patients. Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with pre-existing renal insufficiency, diabetes or advanced vascular disease. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualisation in normal patients.

To avoid contrast induced nephropathy, the following should be considered:
- Identification of high risk patients
- Ensuring adequate hydration. The patient should be hydrated (e.g. at least 100 mL per hour of soft drinks or intravenous saline up to 24 hours after contrast medium administration. In warm areas more fluid should be given).
- 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.
- Monitor renal function (serum creatinine), serum lactic acid and pH of blood.
- Look for symptoms of lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnea, lethargy, diarrhoea and thirst). Blood test results indicative of lactic acidosis: pH<7.25 and lactic acid > 5 mmol.

Paediatrics
In the paediatric population, prolonged fasting and the administration of a laxative before VISIPAQUE injection are to be avoided.

Adequate hydration should be ensured; infants and especially neonates are susceptible to electrolyte disturbance and haemodynamic changes.

Infants - 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 agents and is more commonly observed in neonates and premature infants. Neonates may also be exposed through the mother during pregnancy. Thyroid function in infants exposed to iodinated contrast media (ICM) should be evaluated and monitored. Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of thyroid stimulating hormone (TSH) were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or more than a month. Thyroid function in infants exposed to ICM should therefore be evaluated and monitored until thyroid function is normalised.

Some patients were treated for hypothyroidism.

Risk-benefit should be considered when the following medical problems exist:

Patients with thyrotoxicosis or hyperthyroidism
Iodinated contrast media should not be administered to patients with thyrotoxicosis (see section 4.3).

Special care should be exercised in patients with hyperthyroidism. Patients with manifest but not yet diagnosed hyperthyroidism, patients with latent hyperthyroidism (e.g. nodular goitre) and patients with functional autonomy (ogten 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 should be monitored for the development of thyrotoxicosis in the weeks following 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.

Patients with history of allergic reactions
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. Recent reports of the use of iodinated contrast agents indicate that such pretreatment does not prevent serious life-threatening reactions but may reduce both their incidence and severity.

Patients with multiple myeloma
Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemias, particularly in those with the therapeutically resistant anuria. Although neither the contrast agent nor dehydration have been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication; however, they require special precautions. Preparatory dehydration of these patients is not recommended since it may predispose the patient to precipitation of the myeloma protein in the renal tubules. The presence of myeloma should be considered before instituting intravascular administration of contrast agents.

Patients with phaeochromocytoma
Administration of radiopaque materials to patients known to have, or suspected of having, phaeochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure, and measures for the treatment of hypertensive crisis should be readily available.

Patients with homocystinuria
Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing embolism.

Patients with a history of seizures
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.

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

Diabetic patients treated with metformin
To prevent lactic acidosis, serum creatinine level 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/1.73m^2 (CKD 1 and 2) can continue to take metformin normally.
(2) Patients with eGFR 30-59 mL/min/1.73 m^2 (CKD 3)
- Patients receiving intravenous contrast medium with eGFR equal or greater than 45 mL/min /1.73 m^2) can continue to take metformin normally.
- In patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m^2 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 m^2 (CKD 4 and 5) or with an intercurrent illness causing reduced liver function or hypoxia metformin is contraindicated 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.

Patients with pre-existing renal impairment
A benefit to risk assessment should be made before use of an iodinated contrast medium in patients with pre-existing renal impairment (serum creatinine > 1.5 mg/dL).

Iso-osmolar or low-osmolar contrast media should always be used in these patients.

Contrast medium induced nephrotoxicity
Contrast medium induced nephrotoxicity is a condition in which impaired renal function (an increase in serum creatinine by more than 25% or 44 Dmol/l) occurs within three days following the intravascular administration of a contrast medium in the absence of an alternative aetiology.

Dialysis has been used in the prevention of contrast media induced nephrotoxicity. If clinically indicated, haemodialysis is an effective method for eliminating iodinated contrast medium from the body. Correlating the time of contrast medium to the dialysis schedule is unnecessary, because there is no evidence that haemodialysis protects patients with impaired renal function from contrast media induced nephropathy. The patient should not be re-exposed to contrast media before the kidney function has returned to its previous function. If contrast medium is to be given again, the patient must be adequately hydrated.

Patients on haemodialysis may receive contrast media for radiological procedures.

Complications of catheterisation
In angiographic procedures, the possibility of dislodging plaques, rupturing aneurisms, or damaging or perforating the vessel wall should be borne in mind during catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Non-ionic contrast media have less effect on the coagulation system in vitro, compared to ionic contrast media. For these reasons, meticulous intravascular administration technique is necessary, particularly during angiographic procedures. Close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinised saline solutions, and minimising the length of the procedure may minimise thromboembolic events. Numerous factors, including catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

No safety data have been submitted regarding the following:
- Pregnant and lactating women
- Patients with unstable medical conditions
- Severe pulmonary hypertension
- Uncontrolled arrhythmias
- Decompensated congestive cardiac failure
- Aortic stenosis
- Acute intracranial haemorrhage
- Recent head trauma
- Patients who have had a myocardial infarction in the previous three days

Extravasation:
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 occur within this time. However, experience shows that hypersensitivity reactions may appear up to several hours or days post injection.

Special precautions by indication
Cardioangiography: Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the risk. The inherent risks of angiocardiography in

patients with chronic obstructive pulmonary disease must be weighed against the necessity for performing this procedure.

During left ventriculography and coronary arteriography, vital signs and the ECG should be monitored routinely throughout the procedure. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly.

Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds, because of the haemodynamic changes that may occur after injection into the right heart outflow tract.

Peripheral Arteriography: Pulsation should be present in the artery to be injected. In thromboangiitis obliterans or ascending infection associated with severe ischaemia, arteriography should be performed only if the benefits clearly outweigh the risks.

Visceral Arteriography/Selective visceral i.a. DSA: In thromboangiitis obliterans or ascending infection associated with severe ischaemia, arteriography should be performed only if the benefits clearly outweigh the risks.

Cerebral Arteriography: Cerebral arteriography should be undertaken with extreme care, especially in elderly patients, patients in poor clinical condition, or patients with advanced arteriosclerosis, severe arterial hypertension, cardiac decompensation or recent cerebral embolism or thrombosis.

Since VISIPAQUE is given by rapid injection, the patient should be monitored for possible untoward reactions. In cerebral arteriography, patients should be appropriately prepared consistent with existing or suspected disease states.

In patients with cerebral haemorrhage, a rare association between contrast administration and clinical deterioration, including severe headache and death, has been reported. Therefore, administration of intra-arterial iodinated contrast media in these patients should be undertaken with caution.

Venography: In thromboangiitis obliterans or ascending infection associated with severe ischaemia, venography should be performed only if the benefits clearly outweigh the risks.

Excretory Urography: Urography should be performed with caution in patients with impaired renal function, patients with combined renal and hepatic disease, and patients with diabetic nephropathy.

4.5 Interaction with other medicines and other forms of interaction

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 biguanides/metformin (see section 4.4).

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).

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.

General anaesthesia may be indicated in the performance of some procedures in selected patients. However, a higher incidence of adverse reactions following administration of contrast agents has been reported in anaesthetised patients. This may be attributable either to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anaesthesia, which can reduce cardiac output and increase the duration of exposure to a contrast agent.

Patients using beta blockers may present with atypical symptoms of anaphylaxis which may be misinterpreted as a vagal reaction (see section 4.8).

Addition of an inotropic agent to contrast agents may produce a paradoxical depressant response, which can be deleterious to the ischaemic myocardium.

Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs. Therefore, other pharmaceuticals should not be mixed with contrast agents, including VISIPAQUE, in the same syringe.

Laboratory Tests
Protein-bound iodine (PBI) and total serum organic iodine: transient increases of both tests following urography have been noticed. The results of PBI and radioactive iodine uptake studies which depend on iodine estimations will not accurately reflect thyroid function for up to 16 days following administration of iodinated urographic media. However, thyroid function tests not depending on iodine estimations, such as T_3, resin uptake or free thyroxine assays, are not affected.

VISIPAQUE interferes with Multistix measurements of specific gravity and produces a falsepositive result for protein in the urine via Multistix. However, the Coomassie blue method has been shown to give accurate results for the measurement of urine protein in the presence of VISIPAQUE.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy
Category B1
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.

Reproduction studies have been performed in rats and rabbits at doses up to 2 gI/kg/day and have revealed no evidence of harm to the foetus due to VISIPAQUE. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the drug should be used during pregnancy only if clearly needed.

Labour and delivery
It is not known whether the use of contrast agents during labour or delivery has immediate or delayed effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in Lactation
Occurrence of serious adverse reactions has not been established in nursing infants.

The amount of contrast medium excreted in human milk appears to be low. Breast feeding may be continued normally when iodinated contrast media are given to the mother.

Effects on Fertility
VISIPAQUE did not affect male or female fertility in rats at IV doses up to 2 gI/kg/day.

4.7 Effects on ability to drive and use machines
None known.

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

Serious reactions as well as fatalities are only seen on very rare occasions.

Hypersensitivity reactions usually present as respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus, skin reaction, angioneurotic oedema, hypotension, fever, laryngeal oedema, bronchospasm or pulmonary oedema. 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.

An undesirable effect is said to be:
- very common if its frequency is ≤10%
- common if its frequency is between ≥1% and <10%
- uncommon if its frequency is between ≥0.1% and <1%
- rare if its frequency is between ≥0.01% and <0.1%
- very rare if its frequency is < 0.01%

Reactions, for which no frequency rate can be provided due to lack of clinical data, have been entered with ‘not known’.

The listed frequencies are based on internal clinical documentation and published studies, comprising more than 57,705 patients.

Adults Intravascular use (Intra-arterial and Intravenous use):

MedDRA System Organ Class	**Adverse Drug Reaction (ADR)**	**Frequency**
Endocrine disorders	Hypothyroidism* Transient hypothyroidism	Uncommon Not known
Immune system disorders	Hypersensitivity Anaphylactoid reaction including life-threatening or fatal anaphylaxisAnaphylactoid shock	Uncommon Not known Not known
Psychiatric disorders	Confusional state Anxiety, agitation	Not known Very rare

Nervous system disorders	Headache Dizziness Sensory abnormalities including taste disturbance Paraesthesia Parosmia Motor dysfunction Convulsion Disturbance in consciousness Coma Transient contrast induced encephalopathy which can manifest as sensory, motor or global neurological dysfunction (including amnesia, hallucination, paralysis, paresis, disorientation, transient speech disorder, aphasia, dysarthria)	Uncommon Rare Very rare Rare Rare Not known Not known Not known Not known Not known
Eye disorders	Cortical blindness transient Transient visual impairment (including diplopa, blurred vision) Eyelid oedema	Very rare Very rare Very rare
Cardiac disorders	Arrhythmia (including bradycardia, tachycardia, myocardial infarction) Cardiac arrest, palpitations Cardio-respiratory arrest, spasm of coronary arteriesVentricular hypokinesia Myocardial ischaemia	Rare Very rare Not known Not known Not known
Vascular disorders	Flushing Hypotension Hypertension Ischaemia Arterial spasm Thrombosis Thrombophlebitis Shock	Uncommon Rare Very rare Very rare Not known Not known Not known Not known
Respiratory, thoracic and mediastineal disorders	Cough Sneezing Dyspnoea Throat irritation Laryngeal oedema Pharyngeal oedema Non-cardiogenic pulmonary oedema, bronchospasm Throat tightness	Rare Rare Very rare Very rare Very rare Very rare Not known Not known
Gastrointestinal disorders	Nausea Vomiting Abdominal pain/discomfort, diarrhoea Pancreatitis, salivary gland enlargement	Uncommon Uncommon Very rare Not known

Skin and subcutaneous disorders	Rash or drug eruption Pruritus, urticaria Erythema Angioedema Hyperhidrosis Bullous or exfoliative dermatitis Stevens-Johnson syndrome Erythema multiforme Toxic epidermal necrolysis Acute generalized exanthematous pustulosis Drug rash with eosinophilia and systemic symptoms	Uncommon Uncommon Rare Very rare Very rare Not known Not known Not known Not known Not known Not known
Musculoskeletal, connective tissue and bone disorders	Arthralgia Back pain	Not known Very rare
Renal and urinary disorders	Acute renal injury or nephropathy toxic (CIN) Increased blood creatinine	Uncommon Not known
General disorders and administration site conditions	Feeling hot Chest pain Shivering (chills) Pain and discomfort Administration site reactions including extravasation Pyrexia Feeling cold Asthenic conditions (e.g., malaise, fatigue) Face oedema, localized oedema Swelling	Uncommon Uncommon Rare Rare Rare Rare Rare Very rare Very rare Not known
Injury and poisoning	Iodism	Not known

Paediatrics:

MedDRA System Organ Class	Adverse Drug Reaction (ADR)	Frequency
Endocrine disorders:	Transient hypothyroidism	Not known

In general the type of adverse events reported are similar to those of adults. Although the frequency of events appears to be comparable, the frequency cannot be confirmed because of the different ability of paediatric and adult patients to report adverse events.

The overall character, quality, and severity of adverse reactions in paediatric patients is similar to that reported in adult populations from domestic and foreign postmarketing surveillance and other information. Selected commonly reported adverse events in paediatrics include: vomiting, nausea, fever, rash, pruritus and injection associated discomfort and distress. Diarrhoea and taste perversion were reported in gastrointestinal studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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.

In case of overdose, immediately contact the Poisons Information Centre for advice, in New Zealand, call 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: X-ray contrast media, iodinated. ATC code: V08AB09

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

In a study involving 129 diabetic patients with serum creatinine levels of 1.5 – 3.5 mg/dl, use of VISIPAQUE resulted in 3% of patients experiencing a rise in creatinine of ≥0.5 mg/dl and no patients with a rise of ≥1.0 mg/dl. The peak increase in the serum creatinine concentration within three days after the administration of VISIPAQUE was 0.13 mg per dl (11.2 µmol per litre). A transient increase in tubular enzyme excretion was observed after contrast media injection. However, lower or similar effects on the release of enzymes (alkaline phosphatase and N-acetyl-ß-glucosaminidase) from the proximal tubular cells were observed for VISIPAQUE in comparison to ioxaglate.

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.

Clinical Trials

The safety and efficacy of VISIPAQUE has been established in the paediatric population for arterial studies, for intravenous procedures and gastrointestinal use. Use of VISIPAQUE in these age groups is supported by evidence from adequate and well controlled studies of VISIPAQUE in adults and additional safety data obtained in paediatric studies.

The clinical development of VISIPAQUE comprised: one pharmacokinetic study in 43 subjects and another ten clinical studies to demonstrate efficacy and safety of VISIPAQUE.

Six studies for intavenous use (two urography studies, four CT studies), two studies for intraarterial use (two cardioangiography studies) and two studies for gastrointestinal use. In two of these studies there was a pilot part including 3 and 10 patients, respectively. Otherwise the studies were phase III, randomized, double-blind,parallel-group comparison between iodixanol (VISIPAQUE) and iohexol (OMNIPAQUE).

A total of 638 infants and children were included in the clinical trials. They aged between birth and up to 17 years, 225 of them were younger than 24 months. Of these 403 received iodixanol and 235 patients received iohexol. The patients were equally distributed concerning age, sex

and body weight in all study groups. Neonates were not enrolled in these studies with no child included with body weight <2 kg.

All the intravascular studies (intravenous and intra-arterial) showed that iodixanol was efficacious. No significant differences were detected between the iodixanol and iohexol groups. VISIPAQUE also gave appropriate contrast in all areas of the gastrointestinal tract and was found to be well suited for gastrointestinal examinations in the paediatric population. VISIPAQUE can also be used safely in the paediatric population.

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.

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, de-iodination or biotransformation has been detected in animals.

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 unmetabolised 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.

Paediatric Pharmacokinetics

Forty three (43) paediatric patients <12 years old, with renal function that is normal for their age, received multiple intra-arterial administrations of VISIPAQUE Injection in doses of 0.32 to 3.2 gI/kg body weight. The elimination half-lives for these patients are derived from the mean terminal elimination rate constants (K_{el}): 0.185/hr (newborn to 2 months old), 0.256/hr (2 to <6 months old), 0.299/hr (6 months to <1 year), 0.322/hr (1 to <2 years), and 0.307/hr (2 to <12 years old). The adult mean terminal elimination rate constant is 0.336/hr.

The actual VISIPAQUE clearance and volume of distribution in paediatric patients were not determined. Pharmacodynamic dose adjustments to account for differences in elimination half-life in paediatric patients under 6 months of age have not been studied.

5.3 Preclinical safety data

Carcinogenicity

No long-term animal studies have been performed to evaluate the carcinogenic potential of VISIPAQUE.

Genotoxicity

VISIPAQUE did not induce gene mutation in bacteria or Chinese hamster ovary (CHO) cells in vitro. It was not clastogenic in CHO cells in vitro or in mice in vivo.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

trometamol, sodium chloride, calcium chloride, sodium calciumedetate, hydrochloric acid (pH adjustment), water for injections.

The pH of the product is 6.8 - 7.6.

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Protect vials, bottles and flexible containers of VISIPAQUE from strong daylight and direct exposure to sunlight. Store at controlled room temperature, 15ºC to 30ºC. 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 37ºC for up to one month prior to use. 10 ml and 20 ml polypropylene bottles may be stored at 37ºC 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.

6.5 Nature and contents of container

VISIPAQUE (iodixanol) injection 270 mg I/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 I/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.

6.6 Special precautions for use or disposal

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 (37ºC) 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.

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

9 March 1995

10 DATE OF REVISION OF THE TEXT

11 August 2022
CCSI V5.0

Trademarks
VISIPAQUE is a trademark of GE Healthcare.

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

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Additional data on use with beta blockers added.
4.4	Warning on added.
4.4	Data on hypothyroidism added
4.4	Data on diabetic use added
4.8	Additional adverse events added