GE HEALTHCARE (+ GE logo)

VISIPAQUE™

1 NAME OF THE MEDICINAL PRODUCT

VISIPAQUE 270 mg I/ml, 320 mg I/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	Strength	Content pr. ml.
Iodixanol (INN) Iodixanol (INN)	270 mg I/ml 320 mg I/ml	550 mg equiv. 270 mg I 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 H_2O	Viscosity (mPa·s)	
	37°C	20°C	37°C
270 mg I/ml 320 mg I/ml	290 290	11.3 25.4	5.8 11.4

* Method: Vapour - pressure osmometry.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 INDICATIONS

X-ray contrast medium for use in adults for cardioangiography, peripheral arteriography (conventional and i.a.DSA), abdominal angiography (i.a.DSA), urography, venography and CT-enhancement and for use in children for cardioangiography, urography and CT enhancement. Lumbar, thoracic and cervical myelography.

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.

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		
aortography	270/320 mg I/ml	40-60 ml per inj.
peripheral	270/320 mg I/ml	30-60 ml per inj.
peripheral i.a.DSA	150 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 per inj.
Selective coronary arteriography	320 mg I/ml	4-8 ml per inj.
Children	270/320 mg I/ml	Depending on age, weight and pathology (recommended max total dose 10 ml/kg).

(Table cont. page 3)

Table continued from page 2

Indication/Investigation	Concentration	Volume
Intravenous use		
Urography,		
Adults	270/320 mgI/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 (adults only)		
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.

Elderly: As for other adults.

4.3 CONTRA-INDICATIONS

Manifest thyrotoxicosis. *History of serious hypersensitivity reaction to VISIPAQUE.*

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE.

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_1 and H_2 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 minimize 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 preexisting **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 because there is no evidence that haemodialysis protects patients with impaired renal function from contrast medium induced nephropathy.

The administration of iodinated contrast media may aggravate the symptoms of **myasthenia gravis**. In patients with **phaeochromocytoma** 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 **goiter** 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.

4.5 INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

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.

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 Special warnings and special precautions for use).

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).

4.6 PREGNANCY AND LACTATION

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 fetus, 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.

The degree of excretion into human milk is not known, although expected to be low. Breast feeding should be discontinued prior to administration of VISIPAQUE and should not be recommenced until at least 24 hours after.

4.7 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.**

4.8 UNDESIRABLE 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 minimize 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 nonionic 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 nonionic 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.

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.*

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 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 the patients with a rise of ≥ 1.0 mg/dl. The release of enzymes (alkaline phosphatase and N-acetyl-β-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.

5.3 PRECLINICAL SAFETY DATA

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or teratogenicity due to iodixanol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The following excipients are included: Trometamol, sodium chloride, calcium chloride, sodium calcium edetate, hydrochloric acid (pH adjustment) and 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

See expiry date printed on the label.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

VISIPAQUE should be stored at or below 30°C, protected from light and secondary X-rays. The product can be stored for up to 1 month at 37°C.

6.5 NATURE AND CONTENT OF CONTAINER
Glass vials and bottles:
The product is filled in injection vials (20 ml) and infusion bottles (50, 100, 200 and 500 ml). Both containers are made of colourless highly resistant borosilicate glass (Ph.Eur. Type I), closed with chlorobutyl rubber stoppers (Ph.Eur. Type I), and sealed with complete tear off caps with coloured plastic “flip-off” tops.

Polypropylene bottles:
The product is filled in polypropylene bottles. The bottles of 50 and 100 ml are supplied with a plastic screw cap which is provided with a tamper proof ring.

The product is supplied as:

Glass vials/bottles:

270 mg I/ml:	1 vial of 20 ml
	10 vials of 20ml
	1 bottle of 50 ml
	10 bottles of 50ml
	1 bottle of 100 ml
	10 bottles of 100ml
	1 bottle of 200 ml
	6 bottles of 200ml

	6 bottles of 500 ml
320 mg I/ml:	1 vial of 20 ml 10 vials of 20ml 1 bottle of 50 ml 10 bottles of 50ml 1 bottle of 100 ml 10 bottles of 100ml 1 bottle of 200 ml 6 bottles of 200ml 6 bottles of 500 ml

Polypropylene bottles:

270 mg I/ml	10 x 50 ml 10 x 100 ml
320 mg I/ml	10 x 50 ml 10 x 100 ml

In certain countries some package sizes may not be available.

6.6 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/bottles 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.

NO-0401 OSLO
NORWAY
Phone: +47 23 18 50 50
Fax: +47 23 18 60 00

Co. Cork
IRELAND

Importer:
ELDAN ELECTRONIC INSTRUMENT CO.LTD.

6 Hashiloach Street
P.O.Box 7641
Petach Tiqva 49170
ISRAEL
Tel: 972-3-9371111
Fax: 972-3-9371100

DATE OF (PARTLY) REVISION OF THE TEXT
January 2007

The format of this leaflet has been determined by the Ministry of Health and its contents has been checked and approved – August 2008.