

Not known: Coma, motor dysfunction, disturbance in consciousness, convulsion, transient contrast-induced encephalopathy (including amnesia, hallucination, tremor).

Eye disorders:

Very rare: Transient cortical blindness, visual impairment.

Cardiac disorders:

Rare: Arrhythmia (including bradycardia, tachycardia).

Not known: Cardiac failure, cardiac or cardio- respiratory arrest, myocardial infarction, conduction abnormalities, ventricular hypokinesia, coronary artery thrombosis, angina pectoris, spasms of coronary arteries

Vascular disorders:

Uncommon: Flushing

Rare: Hypotension

Very rare: Hypertension, ischaemia

Not known: Arterial spasm, thrombosis, thrombophlebitis, shock.

Respiratory, thoracic and mediastinal disorders:

Rare: Cough

Very rare: Dyspnoea

Not known: Pulmonary oedema, respiratory arrest, respiratory failure

Gastrointestinal disorders:

Uncommon: Nausea, vomiting

Very rare: Abdominal pain/discomfort

Not known: Acute pancreatitis, pancreatitis aggravated, salivary gland enlargement

Skin and subcutaneous system disorders

Uncommon: Rash, pruritus, urticaria

Very rare: angioedema, erythema

Not known: Bullous dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, drug eruption, dermatitis allergic, skin exfoliation

Musculoskeletal and connective tissue disorders:

Very rare: Back pain, muscle spasm

Not known: Arthralgia

Renal and urinary disorders:

Very rare: Impairment of renal function including acute renal failure

General disorders and administration site conditions:

Uncommon: Feeling hot, chest pain

Rare: Pain, discomfort, shivering (chills), pyrexia, administration site reactions including extravasation

Very rare: Feeling cold, asthenic conditions (e.g. malaise, fatigue)

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: Dizziness, transient contrast induced encephalopathy (including amnesia, hallucinations, confusion.

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

Not known: 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

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_{1/2} ~ 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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: X-ray contrast medium, iodinated ATC nr: 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 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.

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 extracellular 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.

Preclinical safety data

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

Pharmaceutical particulars

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.

Incompatibilities

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

Shelf life

See expiry date printed on label.

Special precautions for storage

VISIPAQUE should be stored at up to 30°C protected from light. The product in glass containers and polypropylene bottles may be stored at 37°C for up to 1 month prior to use.

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, 75, 100, 150, 175, 200 and 500 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 mgI/ml:	10 vials of 20 ml
	10 bottles of 50 ml
	10 bottles of 100 ml
	6 bottles of 200 ml

320 mgI/ml:	10 vials of 20 ml
	10 bottles of 50 ml
	10 bottles of 100 ml
	6 bottles of 200 ml

Polypropylene bottles

270 mgI/ml:	10 bottles of 50 ml
	10 bottles of 75 ml
	10 bottles of 100 ml
	10 bottles of 150 ml
	10 bottles of 175 ml
	10 bottles of 200 ml
	6 bottles of 500 ml

320 mgI/ml:	10 bottles of 50 ml
	10 bottles of 75 ml
	10 bottles of 100 ml
	10 bottles of 150 ml
	10 bottles of 175 ml
	10 bottles of 200 ml
	6 bottles of 500 ml

In certain countries some package sizes may not be available.

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.

GE Healthcare AS	Manufactured by:
Nycoveien 1-2	GE Healthcare Ireland Limited
P.O. Box 4220 Nydalen	IDA Business Park
NO-0401 OSLO	Carrigtohill
NORWAY	Co. Cork
Phone +47 23 18 50 50	Ireland
Fax +47 23 18 60 00	

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