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GE Healthcare

VISIPAQUE™

IODIXANOL

NAME OF THE MEDICINAL PRODUCT

Visipaque 270 mg I/ml and 320 mg I/ml

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Concentration	Osmolality * mOsm/kg H_2O	Viscosity (mPa·s)	
	37°C	20°C	37°C
270 mg I/ml	290	11.3	5.8
320 mg I/ml	290	25.4	11.4

* Method: Vapour - pressure osmometry.

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

Indications

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

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

[1] Both strengths are documented, but 270 mg I/ml is recommended in most cases.
[2] 80 ml may be exceeded in selected cases.
[3] To minimize possible adverse reactions a total dose of 3.2 g iodine should not be exceeded.

Elderly: As for other adults

Contraindications

Hypersensitivity to the active substance or to any of the excipients. Manifest thyrotoxicosis.

Special warnings and 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.

Patients using beta blockers may present with atypical symptoms of hypersensitivity which may be misinterpreted as a vagal reaction.

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.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiocardiographic procedures with both ionic and non-ionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended, including close attention to guide wire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing (e.g.) with heparinized saline solutions), and minimizing the length of the procedure so as to minimise the risk of procedure.

Encephalopathy has been reported with the use of iodixanol (see section Undesirable effects). 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.

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 frequentl y (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 to seizures and merit particular care.
Also alcoholics and drug addicts have an increased risk of 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, , 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.

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.

(1) Patients with eGFR equal or greater than 60 mL/min/1.73m² (CKD 1 and 2) can continue to take metformin normally.

(2) Patients with eGFR 30-59 mL/min/1.73 m² (CKD 3)

- Patients receiving intravenous contrast medium with eGFR equal or greater than 45 mL/min /1.73 m²) 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 m² metformin should be discontinued 48 hours before contrast medium and should only be restarted 48 hours after contrast medium if renal function has not deteriorated.

(3) In patients with eGFR less than 30 mL/min/1.73 m² (CKD 4 and 5) or with an intercurrent illness causing reduced liver function or hypoxia metformin is contraindicated 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.

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.

Patients with manifest but not yet diagnosed hyperthyroidism, patients with latent hyperthyroidism (e.g., nodular goitre) and patients with functional autonomy (often e.g. elderly patients, especially in regions with iodine deficiency) are at higher risk of acute thyrotoxicosis after use of iodinated contrast media. The additional risk should be evaluated in such patients before use of an iodinated contrast medium. Testing of thyroid function prior to contrast medium administration and/or preventative thyreostatic medication may be considered in patients with suspected hyperthyroidism. The patients at risk should be monitored for the development of thyrotoxicosis in the weeks following the injection.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism.

Special attention should be paid to pediatric patients below 3 years of age because an incident underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. The incidence of hypothyroidism in patients younger than 3 years of age exposed to iodinated contrast media has been reported between 1.3% and 15% depending on the age of the subjects and the dose of the iodinated contrast agent and is more commonly observed in neonates and premature infants. Neonates may also be exposed through the mother during pregnancy. Thyroid function should be evaluated in all pediatric patients younger than 3 years of age following exposure to iodinated contrast media. If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalized.

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 injections.
Advanced life support facilities should be readily available.

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 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.

Interaction with other medicinal products 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 metformin (see 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).

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

High concentrations of contrast medium 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.

Pregnancy and lactation

In neonates who have been exposed to iodinated contrast
media in utero, it is recommended to monitor thyroid function (see section Special warnings and precautions for use).
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.

Effects on ability to drive and use machines

No studies on the ability to drive or use machines have been performed. However, it is not advisable to drive a car or use machines during the first 24 hours following intrathecal procedure (see Special warnings and special precautions for use).

Undesirable effects

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

Undesirable effects associated with VISIPAQUE are usually mild to moderate and transient in nature. Serious reactions as well as fatalities are only seen on very rare occasions.

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

They may appear either immediately after the injection or up to a few days later. Hypersensitivity reactions may occur irrespectively of the dose and mode of administration and mild symptoms may represent the first signs of a serious anaphylactoid reaction/shock.

Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the vascular access. Patients using beta blockers may present with atypical symptoms of hypersensitivity which may be misinterpreted as a vagal reaction.
A minor transient increase in serum creatinine is common after iodinated contrast media, but is usually of no clinical relevance.

The frequencies of undesirable effects are defined as follows:
Very common (≥1/10), common ((≥1/100 to < 1/10), uncommon((≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

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

Intravascular administration:

Immune system disorders:
Uncommon: Hypersensitivity
Not known: Anaphylactoid reaction, anaphylactoid shock; including life-threatening or fatal anaphylaxis

In patients with autoimmune diseases cases of vasculitis and Steven- Johnson like syndrome were observed.

Endocrine disorders:
Not known: Hyperthyroidism, transient hypothyroidism.

Psychiatric disorders:
Not known: Confusional state
Very rare: Anxiety, agitation

Nervous system disorders:
Uncommon: Headache
Rare: Dizziness, sensory abnormalities including taste disturbance, paraesthesia, parosmia
Very rare: Syncope, tremor (transient), hypoesthesia
Not known: Coma, disturbance in consciousness, seizures, transient contrast-induced encephalopathy caused by extravasation of contrast media, which can manifest as sensory, motor or global neurological dysfunction (including amnesia, hallucination, paralysis, paresis, disorientation, transient speech disorder, aphasia, dysarthria)

Eye disorders:
Very rare: Cortical blindness (transient), transient visual impairment (including diplopia, blurred vision), eyelid oedema

Cardiac disorders:
Rare: Arrhythmia (including bradycardia, tachycardia), myocardial infarction, cardiac depression
Very rare: Cardiac arrest, palpitations
Not known: Ventricular hypokinesia, spasms of coronary arteries, cardio-respiratory arrest

Vascular disorders:
Uncommon: Flushing
Rare: Hypotension
Very rare: Hypertension
Not known: Shock, arterial spasm

Respiratory, thoracic and mediastinal disorders:
Uncommon: Nausea, vomiting
Rare: Cough, sneezing
Very rare: Dyspnoea, throat irritation, laryngeal oedema, pharyngeal oedema
Not known: Non-cardiogenic pulmonary oedema, bronchospasm, throat tightness

Gastrointestinal disorders:
Uncommon: Nausea, vomiting
Very rare: Abdominal pain, diarrhoea
Not known: Pancreatitis, salivary gland enlargement

Skin and Subcutaneous Tissue Disorders:
Uncommon: Rash or drug eruption, pruritus, urticaria
Rare: Erythema
Very rare: Angioedema, hyperhidrosis
Not known: Bullous or exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms

Musculoskeletal and connective tissue disorders:
Very rare: Back pain

Renal and urinary disorders:
Uncommon: Acute kidney injury or nephropathy toxic (CIN)
Not known: Increased blood creatinine

General disorders and administration site conditions:
Uncommon: Feeling hot, chest pain
Rare: Shivering (chills), pyrexia, pain and discomfort administration site reactions including extravasation, feeling cold
Very rare: Asthenic conditions (e.g., malaise, fatigue), face oedema, localized oedema
Not known: Swelling

Injury, poisoning and procedural complications:
Not known: Iodism

Peripheral angiography:
Heat sensation in peripheral angiography is very common
(Incidence: >1:10), while distal pain occurs commonly
(Incidence <1:10, but >1:100).

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.

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.
Immnue system disorders:
Not known: Hypersensitivity, including anaphylactic/ anaphylactoid reactions

Nervous system disorders:
Uncommon: Headache (may be severe and lasting after intrathecal use)
Not known: Dizziness (after intrathecal use), transient contrast-induced encephalopathy caused by extravasation of contrast media, which can manifest as sensory, motor or global neurological dysfunction (including amnesia, hallucination, confusional state, paralysis, paresis, disorientation, aphasia, speech disorder (after intrathecal use).

Gastrointestinal disorders:
Very common: Vomiting
Not known: Nausea, abdominal pain (after hysterosalpingography)

General disorders and administration site conditions:
Not known: Shivering, pain at injection site

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 (t½ ~ 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.

PHARMACOLOGICAL PROPERTIES

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-s-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 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. Approximatel y 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.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction.

PHARMACEUTICAL PARTICULARS

List of excipients

The following excipients are included: Trometamol, sodium chloride, calcium chloride dihydrate, 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.

Nature and content of container

Glass vials and bottles:
The product is filled in injection vials (20 ml) and infusion bottles (100 ml). Both containers are made of colourless highly resistant borosilicate glass (Ph.Eur. Type I), closed with chlorobutyl or bromobutyl rubber stoppers (Ph.Eur. Type I), and sealed with complete tear off caps with coloured plastic "flip-off" tops.

The product is supplied as:

Glass vials/bottles
270 mgI/ml: 10 vials of 20 ml
320 mgI/ml: 10 bottles of 100 ml

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.

Manufactured by:
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