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INFORMATION FOR THE HEALTHCARE PROFESSIONAL

VISIPAQUE™

IODIXANOL

1 NAME OF THE MEDICINAL PRODUCT

VISIPAQUE 270 mg I/ml and 320 mg I/ml Solution for Injection, glass container and polypropylene container

2 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 37°C	Viscosity (mPa•s)	
		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.

270 mg I/ml: This medicinal product contains 0.76 mg (0.03 mmol) sodium per ml. To be taken into consideration by patient on a controlled sodium diet.

320 mg I/ml: This medicinal product contains 0.45 mg (0.02 mmol) sodium per ml. To be taken into consideration by patient on a controlled sodium diet (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

VISIPAQUE is supplied ready to use as clear, colourless to pale yellow aqueous solutions.

4 CLINICAL PARTICULARS

4.1 Indications

This medicinal product is for diagnostic use only.

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. Arthrography, hysterosalpingography (HSG) and studies of the gastrointestinal tract. In children it is used for cardioangiography, urography, CT-enhancement and studies of the upper gastrointestinal tract.

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, and for use in body cavities.

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** **Adults** 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	320 mg I/ml	Depending on age, weight and pathology (recommended max total dose 10 ml/kg)

[1] Both strengths are documented, but 270 mg I/ml is recommended in most cases.

Indication/Investigation	Concentration	Volume
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 **Adults**	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 **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] 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.

Indication/Investigation	Concentration	Volume
Use in body cavities		The dosage must be adjusted individually to allow optimal visualisation
Adults **Arthrography**	270 mg I/ml	1 – 15 ml
Hysterosalpingography (HSG)	270 mg I/ml	5 – 10 ml The recommended dose may be exceeded several times due to e.g. backflow into the vagina (up to 40 ml has been studied).
Gastrointestinal studies **Oral use** Adults Small bowel follow through	320 mg I/ml	80 – 200 ml has been studied
Oesophagus	320 mg I/ml	10 – 200 ml has been studied
Stomach	320 mg I/ml	20 – 200 ml has been studied
Children	320 mg I/ml	5 ml/kg b.w. 10-240 ml has been studied
Rectal use Children	270/320 mg I/ml	30 – 400 ml has been studied

For elderly patients, patients with hepatic and/or renal impairments, the usual/proposed doses for adults can be used.

4.3 Contraindications

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

4.4 Special warnings and precautions for use.

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

Hypersensitivity:
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 remote. 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 possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/ anaphylactoid reactions should always be considered. The majority of serious undesirable occur within the first 30 minutes. Late onset (that is 1 hour or more after application) hypersensitivity reactions can occur. Advanced life support facilities should be readily available.

Patients should be observed for at least 30 minutes after administration of VISIPAQUE.

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.

Coagulopathy:
Non-ionic, iodinated contrast media inhibit blood coagulation in vitro less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing contrast media including non-ionic media. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angio-cardiographic 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 minimize the risk of procedure-related thrombosis and embolism.

Care should be taken in patients with homocystinuria. (risk for thromboembolism).

Hydration
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.

Cardio-circulatory reactions
Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias. Rarely severe life-threatening reactions and fatalities of cardiovascular origin such as cardiac-, cardio-respiratory arrest and myocardial infarction have occurred.

CNS disturbances
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. 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. In regard to intravascular application care should be taken in patients with acute stroke or acute intracranial bleeding, in patients with altered blood brain barrier, cerebral oedema or acute demyelinisation.

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

Renal reactions
Major risk factor for contrast medium-induced nephropathy is underlying renal dysfunction.

Diabetes mellitus and the volume of iodinated contrast medium administered are contributing factors in the presence of renal dysfunction. Additional concerns are dehydration, advanced arteriosclerosis, poor renal perfusion and the presence of other factors that may be nephrotoxic, such as certain medications or major surgery.
To prevent acute renal failure following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk. Patients with paraproteinemias (myelomatosis and Waldenström's macroglobulinemia) are also at risk.

Preventive measures include:
- Identification of high risk patients
- Ensuring adequate hydration. If necessary by maintaining an i.v. infusion from before the procedure until the contrast medium has been cleared by the kidneys.
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, or major surgery, until the contrast medium has been cleared.
- Dose reducing to a minimum.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

Iodinated contrast agents can be used by patients on haemodialysis as the agents are removed by the dialysis process.

Diabetic patients receiving metformin:
There is a risk of the development of lactic acidosis when iodinated contrast agents are administered to diabetic patients treated with metformin, particularly in those with impaired renal function. To prevent lactic acidosis, the serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast media

(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/1.73m² (CKD 3)
- Patients receiving intravenous contrast medium with eGRF equal or greater than 45 mL/min /1.73m²) 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/1.73m² 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/1.73m² (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 cases where renal function is impaired or unknown, the physician should evaluate the risk/benefit of the contrast medium examination, and the following precautions should be implemented: Metformin should be stopped. The patient should be fully hydrated prior to contrast medium administration and for 24 hours afterwards. Renal function (e.g. serum creatinine), serum lactic acid and blood pH should be monitored. A pH< 7.25 or a lactic acid level of > 5 mmol/litre are indicative of lactic acidosis. The patient should be observed for symptoms of lactic acidosis. These include vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea and thirst.

Impaired renal and hepatic function
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.

Myasthenia gravis
The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis.

Phaeochromocytoma
In patients with phaeochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis.

Disturbances in thyroid function
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 of 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.

Paediatric population
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 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 paediatric 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
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. The patient should remain in the hospital environment (but not necessarily the radiology department) for one hour after the last injection, and should return to the radiology department if any symptoms develop.

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.

Hysterosalpingography
Hysterosalpingography should not be performed during pregnancy or in the presence of acute pelvic inflammatory disease (PID).

4.5 Interaction with other medicinal products 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).

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

There is some evidence that use of beta blockers is a risk factor for anaphylactoid reactions to X-ray contrast media (severe hypotension has been seen with X-ray contrast media on beta blocker therapy).

Document: 1209858 GBR Version: 0

1209858 GBR

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PACKAGE LEAFLET: INFORMATION FOR THE USER

VISIPAQUE™

IODIXANOL

Visipaque 270 mg I/ml solution for injection
Visipaque 320 mg I/ml solution for injection
iodixanol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you:
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What Visipaque is and what it is used for

This medicine is for diagnostic use only. It is used only to help identify an illness.
Visipaque is a 'contrast medium'. It is given before an X-ray to make the picture that your doctor takes clearer.
- Once injected, it can help your doctor tell apart normal or abnormal appearance and shape of some organs in your body.
- It can be used for X-rays of your urinary system, spine or blood vessels, including blood vessels of your heart.
- Some other people are given this medicine before or during a scan of their head or body using 'computed tomography' (also called a CAT scan). This type of scan uses X-rays.
- It can also be used to look at your gullet (oesophagus), stomach and intestine, or for looking in body cavities, such as in your joints or womb and ovarian tubes.

Your doctor will explain which part of your body will be scanned.

2. What you need to know before you use Visipaque

Do not use Visipaque:
- If you suffer from severe thyroid problems.
- If you are allergic (hypersensitive) to iodixanol or any of the other ingredients of Visipaque (listed in section 6).

Warnings and precautions
Check with your doctor before having Visipaque:
- If you have ever had an allergic reaction after a medicine similar to Visipaque, called a 'contrast medium'.
- If you have any thyroid problems.
- If you have ever had any allergies.
- If you have asthma.
- If you have diabetes.
- If you have any brain disease or tumours.
- If you have severe heart disease.
- If you have kidney problems, or both liver and kidney problems.
- If you have an illness called 'myasthenia gravis' (a condition causing severe muscle weakness).
- If you have 'phaeochromocytoma' (constant or attacks of high blood pressure due to a rare tumour of your adrenal gland).
- If you have "homocystinuria" (a condition with increased excretion of the amino acid cysteine in urine)
- If you have any problems with your blood or your bone marrow.
- If you have ever been dependent on alcohol or drugs.
- If you have epilepsy.
- If you are having a thyroid function test in the next few weeks.
- If you are having blood or urine samples taken on the same day.

If you are not sure if any of the above apply to you, talk to your doctor before having Visipaque.

During or shortly after the imaging procedure you may experience a short-term brain disorder called encephalopathy. Tell your doctor straight away if you notice any of the symptoms related to this condition described in Section 4.
Thyroid disorders may be observed following administration of Visipaque in both children and adults. Infants may also be exposed through the mother during pregnancy. Your doctor may need to perform thyroid function tests before and/or after the administration of Visipaque.

Other medicines and Visipaque
Tell your doctor if you are taking, have recently taken or might take other medicines.
This includes medicines obtained without a prescription or medicines bought abroad.
Tell your doctor if you
- Take metformin for diabetes
- Take medicine to inhibit the immune defence, e.g. in connection with transplantation (interleukin-2).
- Take medicines to lower the blood pressure (beta blockers)

Pregnancy, breast-feeding and fertility
You must tell your doctor if you are pregnant or think you may be pregnant. Your doctor will only use this product if it is considered that the benefit outweighs the risk.
If Visipaque has been given to the mother during pregnancy, it is recommended to monitor the infants thyroid function.
Breast-feeding may be continued normally after an examination with Visipaque.

Driving and using machines
Do not drive or use tools or machines after your last injection of Visipaque for:
- 24 hours after an injection into your skull or spinal cord (intratheca examination)
- one hour in all other cases.

This is because you may feel dizzy or have other signs of a reaction afterwards.

Important information about the amount of the sodium content in Visipaque
Visipaque contains sodium. The amount present will depend on what kind of examination you will have.
You must tell your doctor if you are on a diet that should not contain sodium or are on a sodium controlled (salt restricted) diet.

3. How to use Visipaque

Visipaque will always be given to you by a specially trained and qualified person.
- Visipaque will always be used in a hospital or clinic.
- They will tell you anything you need to know for its safe use.

Your doctor will decide the dose that is best for you.

The usual dose is:
- One single injection or you may be asked to swallow it. If you are a child you can get it rectally.

After you have been given Visipaque
You will be asked:
- to drink plenty of fluids afterwards (to help flush the medicine from your body), and
- to stay in or around the area where you had your scan or X-ray for around 30 minutes, and to stay in the clinic or hospital for one hour.

If you have any side effects during this time, tell your doctor straight away (see section 4 "Possible side effects").
The advice above applies to **all patients** who have had Visipaque. If you are not sure about any of the above ask your doctor.

Visipaque may be given in lots of different ways, a description of the ways it is usually given can be found below:

Injection into an artery or vein
Visipaque will most commonly be injected into an arm vein or leg vein. Sometimes it will be given through a thin plastic tube (catheter), inserted into an artery usually in your arm or groin.

Injection into your spine
Visipaque will be injected into the space around your spinal cord to see your spinal canal.
If you have been given Visipaque into your spine afterwards you will be asked to follow the advices below:
- to rest with your head and body upright for one hour, or six hours if you stay in bed, and
- to walk carefully and try not to bend down for six hours, and
- not to be completely alone for the first 24 hours after having Visipaque, if you are an outpatient and have ever had fits.

The advice above applies only if you have had Visipaque *injected into your spine*. If you are not sure about any of the above ask your doctor.

Use in your body cavities or joints
Body cavities may be the joints, uterus and ovarian tubes. How and where Visipaque is given will vary.

Use by mouth
For examination of the gullet, stomach or small bowel, Visipaque is normally given by mouth. Visipaque may be diluted with water for these examinations.

4. Possible side effects

Like all medicines this medicine can cause side effects, although not everybody gets them.

Allergic reactions
If you have an allergic reaction when you are in hospital or a clinic having Visipaque, tell the doctor straight away.
The signs may include:
- wheeziness, difficulty breathing, or tightness or pain in your chest
- skin rash, lumps, itchy spots, blisters on skin and in mouth, or other allergic symptoms
- swelling of your face
- dizziness or fainting (caused by low blood pressure)

The above side effects may happen several hours or days after Visipaque is given. If any of these side effects happen after you leave the hospital or clinic, go straight to the casualty department of your nearest hospital.

Other side effects that you may have are listed below, these depend on how or why Visipaque was given to you. Ask your doctor if you are not sure how you were given Visipaque.

Turn over ▶

After an injection into an artery or vein

Uncommon (affects less than 1 in 100 people)
- allergic reaction also known as hypersensitivity reaction, see "Allergic reactions" above for the signs
- headache,
- flushing
- nausea, vomiting
- feeling hot
- chest pain
- kidney problems

Rare (affects less than 1 in 1,000 people)
- feeling dizzy, irregular heartbeats, low blood pressure,
- sense things differently (including different taste, or different smell, tingling or numbness or burning sensation)
- reddening of the skin
- heart attack
- cough, sneezing
- shivers, fever, feeling cold
- pain and discomfort, local reactions (where it was injected)

Very rare (affects less than 1 in 10,000 people)
- feeling agitated
- anxiety
- stroke
- fainting
- high blood pressure
- difficulty breathing, throat irritation, swelling of your throat
- pain or discomfort around your stomach area (abdominal pain)
- arrest of the heart
- short term memory loss
- unease
- tiredness
- back pain
- muscle spasm
- decreased blood supply (ischaemia)
- temporary blindness
- transient reduced eyesight (including double vision, unclear vision)
- swelling of the eyelids
- swelling of the face or localised swelling

Unknown (the number of people affected is not known)
- allergic reaction, allergic shock leading to shock and collapse, see "Allergic reactions" above for the other signs
- feeling confused
- coma
- difficulty moving around for a while
- cramps
- blood clots (thrombosis)
- swelling, pain and swelling of your vein
- severe breathing difficulties (due to fluid in your lungs), stopped breathing
- pancreatic problems (acute or worsening inflammation of the pancreas)
- enlarged salivary gland (swelling and tenderness (pain) of your saliva glands)
- pain in your joints
- heart and lung arrest
- Short term brain disorders (encephalopathy) which can cause confusion, memory loss, hallucinations difficulties with vision, loss of vision, seizures, loss of coordination, loss of movement in one side of the body, problems with speech, and loss of consciousness.
- including hallucinations seizures (fits)
- increased creatinine in a test meaning problems with your kidneys
- iodine poisoning (iodism)

After an injection into your spine

Uncommon (affects less than 1 in 100 people)
- headache (may be severe and lasting for hours)
- vomiting

Unknown (the number of people affected is not known)
- feeling dizzy
- nausea
- shivering
- pain (where it was injected)
- allergic reaction, see "Allergic reactions" above for the signs
- Short term brain disorders (encephalopathy) including feeling confused, memory loss, hallucinations difficulties with vision, loss of vision, seizures, loss of coordination, loss of movement in one side of the body, problems with speech, and loss of consciousness.
- muscle spasm

After use in body cavities

(such as uterus and ovarian tubes)

Very common (affects more than 1 in 10 people)
- pain around your stomach area
- bleeding from your vagina

Common (affects less than 1 in 10 people)
- headache, feeling sick (nausea), high temperature

Unknown (the number of people affected is not known)
- vomiting
- shivering
- local reactions (where it was injected)
- allergic reaction, see "**Allergic reactions**" above for the signs

After injection into your joints

Common (affects less than 1 in 10 people)
- pain where it was injected

Unknown (the number of people affected is not known)
- shivering
- allergic reactions, see "**Allergic reactions**" above for the signs

After being given it by mouth

Common (affects less than 1 in 10 people)
- diarrhoea, feeling sick (nausea)
- pain around your stomach area

Uncommon (affects less than 1 in 100 people)
- vomiting

Unknown (the number of people affected is not known)
- shivering
- allergic reaction, see "Allergic reactions" above for the signs

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at the website: https://yellowcard.mhra.gov.uk/.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Visipaque

- Keep out of sight and reach of children.
- Do not use Visipaque after the expiry date which is stated on the label EXP.
- Store in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Visipaque contains

The active substance is iodixanol.
Visipaque 270 mg I/ml contains 550 mg iodixanol per ml (equivalent to 270 mg iodine per ml).
Visipaque 320 mg I/ml contains 652 mg iodixanol per ml (equivalent to 320 mg iodine per ml).
The other ingredients are small amounts of trometamol, sodium chloride, calcium chloride dihydrate, sodium calcium edetate, hydrochloric acid (for pH adjustment), and water.

What Visipaque looks like and contents of the pack

Visipaque is a solution for injection. The product is a clear, colourless to pale yellow, aqueous solution.
Visipaque is supplied as:

270 mg I/ml:

10 vials of 20 ml
10 bottles of 50 ml
10 bottles of 75 ml
1 bottle of 100 ml
10 bottles of 100 ml
1 bottle of 200 ml
6 bottles of 200 ml
1 polypropylene bottle of 50 ml
10 polypropylene bottles of 50 ml
1 polypropylene bottle of 75 ml
10 polypropylene bottles of 75 ml
1 polypropylene bottle of 100 ml
10 polypropylene bottles of 100 ml
1 polypropylene bottle of 150 ml
10 polypropylene bottles of 150 ml
1 polypropylene bottle of 175 ml
10 polypropylene bottles of 175 ml
1 polypropylene bottle of 200 ml
10 polypropylene bottles of 200 ml
6 polypropylene bottles of 500 ml

320 mg I/ml:

10 vials of 20 ml
10 bottles of 50 ml
1 bottle of 100 ml
10 bottles of 100 ml
1 bottle of 200 ml
6 bottles of 200 ml
1 polypropylene bottle of 50 ml
10 polypropylene bottles of 50 ml
1 polypropylene bottle of 75 ml
10 polypropylene bottles of 75 ml
1 polypropylene bottle of 100 ml
10 polypropylene bottles of 100 ml
1 polypropylene bottle of 150 ml
10 polypropylene bottles of 150 ml
1 polypropylene bottle of 175 ml
10 polypropylene bottles of 175 ml
1 polypropylene bottle of 200 ml
10 polypropylene bottles of 200 ml
6 polypropylene bottles of 500 ml

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
GE Healthcare AS
Nycoveien 1
0485 Oslo
Norway

Manufacturer:
GE Healthcare AS
Nycoveien 1
0485 Oslo
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or
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4.6 Fertility, Pregnancy and lactation

Pregnancy:
The safety of VISIPAQUE for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development.

Since, wherever possible, radiation exposure should be avoided during pregnancy, the benefits of any X-ray examination, with or without contrast media, should be carefully weighed against the possible risk. The product should not be used in pregnancy unless benefit outweighs risk and it is considered essential by the physician.

In neonates who have been exposed to iodinated contrast media in utero, it is recommended to monitor thyroid function (see section 4.4).

Breast-feeding:
Contrast media are poorly excreted in human breast milk and minimal amounts are absorbed by the intestine. Breast feeding may be continued normally when iodinated contrast media are given to the mother.

4.7 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 for one hour after the last injection or during the first 24 hours following intrathecal examination (see section 4.4).

4.8 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, these may include acute-on-chronic renal failure, acute renal failure, anaphylactic or anaphylactoid shock, hypersensitivity reaction followed by cardiac reactions (Kounis' syndrome), cardiac or cardio-respiratory arrest and myocardial infarction. Cardiac reaction may be promoted by the underlying disease or the procedure.

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

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

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 574,705 patients.

Intravascular administration:
Blood and lymphatic system disorders
Not known: Thrombocytopenia

Immune system disorders:
Uncommon: Hypersensitivity
Not known: Anaphylactic/anaphylactoid shock, anaphylactic/ anaphylactoid reaction including life-threatening or fatal anaphylaxis

Endocrine disorders:
Not known: Hyperthyroidism, transient hypothyroidism

Psychiatric disorders:
Very rare: Agitation, anxiety
Not known: Confusional state

Nervous system disorders:
Uncommon: Headache
Rare: Dizziness, sensory abnormalities including taste disturbance, paraesthesia, parosmia
Very rare: Cerebrovascular accident, amnesia, syncope.
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 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
Very rare: Cardiac arrest, palpitation
Not known: Cardio-respiratory arrest,, ventricular hypokinesia, myocardial ischaemia, conduction abnormalities, coronary artery thrombosis, angina pectoris, spasm 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, sneezing
Very rare: Dyspnoea, throat irritation, laryngeal oedema, pharyngeal oedema
Not known: Non-cardiogenic pulmonary oedema, respiratory arrest, respiratory failure, bronchospasm, throat tightness.

Gastrointestinal disorders:
Uncommon: Nausea, vomiting
Very rare: Abdominal pain/discomfort, diarrhoea
Not known: Acute pancreatitis, pancreatitis aggravated, salivary gland enlargement

Skin and subcutaneous system 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, dermatitis allergic

Musculoskeletal and connective tissue disorders:
Very rare: Back pain, muscle spasm
Not known: Arthralgia

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: Pain and discomfort, shivering (chills), pyrexia, administration site reactions including extravasation, feeling cold
Very rare: Asthenic conditions (e.g. malaise, fatigue), face oedema, localised oedema
Not known: Swelling

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 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

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, injection site reaction

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

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at the website: https://yellowcard.mhra.gov.uk/.

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, treatment of overdose is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 64 diabetic patients with serum creatinine levels of 115 - 308 µmol/L, VISIPAQUE use resulted in 3% of patients experiencing a rise in creatinine of ≥44.2 µmol/Land 0% of patients with a rise of ≥88.4 µmol/L. The release of enzymes (alkaline phosphatase and N-acetyl-ß-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.

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 in normal adults. In infants
the elimination of iodixanol is prolonged ($t_{½}$ approx. 4 hours in newborns). 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.

After intrathecal administration the half-life of iodixanol is prolonged reflecting the rate of elimination from the central nervous system compartment into systemic circulation. The apparent elimination half-life varies, but with a mean value around 12 hours.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are included:
Trometamol,
Sodium chloride,
Calcium chloride dihydrate,
Sodium calcium edetate,
Hydrochloric acid (pH adjustment),
Water for injections.
The pH of the product is 6.8 - 7.6.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. A separate syringe should be used.

6.3 Shelf life

The shelf life is 3 years.
In-use shelf-life: The iodixanol solution in the 500 ml polypropylene bottles is chemically stable for 24 hours after opening.

6.4 Special precautions for storage

Keep the container in the outer carton. The product in glass containers and 40, 50, 75, 100, 150, 175, 200 and 500 ml in polypropylene bottles can be stored for up to 1 month at 37 °C, protected from light.

6.5 Nature and content of container

Glass containers:
The product is filled in injection vials (20 ml) and infusion bottles (50, 75, 100, and 200 ml). The glass vials/bottles containers are made of colourless highly resistant borosilicate glass (Ph.Eur. Type I), closed with halobutyl 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 closed with halobutyl rubber stoppers (Ph.Eur. Type I), and supplied with a screw cap which is provided with a tamper proof ring.

The product is supplied as:
270 mg I/ml:

10 vials of 20 ml
10 bottles of 50 ml
10 bottles of 75 ml
1 bottle of 100 ml, 10 bottles of 100 ml
1 bottle of 200 ml, 6 bottles of 200 ml

320 mg I/ml:

10 vials of 20 ml
10 bottles of 50 ml
1 bottle of 100 ml, 10 bottles of 100 ml
1 bottle of 200 ml, 6 bottles of 200 ml

Polypropylene Containers:

270 mg I/ml:
Bottles with rubber stopper and plastic screw cap:

1 bottle of 50 ml, 10 bottles of 50 ml
1 bottle of 75 ml, 10 bottles of 75 ml
1 bottle of 100 ml, 10 bottles of 100 ml
1 bottle of 150 ml, 10 bottles of 150 ml
1 bottle of 175 ml, 10 bottles of 175 ml
1 bottle of 200 ml, 10 bottles of 200 ml
6 bottles of 500 ml (multi-dose)

320 mg I/ml:
Bottles with rubber stopper and plastic screw cap:

1 bottle of 50 ml, 10 bottles of 50 ml
1 bottle of 75 ml, 10 bottles of 75 ml
1 bottle of 100 ml, 10 bottles of 100 ml
1 bottle of 150 ml, 10 bottles of 150 ml
1 bottle of 175 ml, 10 bottles of 175 ml
1 bottle of 200 ml, 10 bottles of 200 ml
6 bottles of 500 ml (multi-dose)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Like all parenteral products, Visipaque should be inspected visually for particulate matter,
discolouration and the integrity of the container prior to use.
Visipaque may be warmed to body temperature (37°C) before administration. Any unused
product or waste material should be disposed of in accordance with local requirements.

Glass vials/bottles and polypropylene bottles up to 200 ml
The product should be drawn into the syringe immediately before use. For single use only, any unused portions must be discarded.

Polypropylene bottles of 500 ml
The iodixanol solution in the 500 ml polypropylene bottles is chemically stable for 24 hours. From a microbiological point of view, the product should be used immediately after opening. If not used immediately after opening, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours, unless opening has taken place under controlled and validated aseptic conditions.
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. Remove the plastic screw cap by tearing off the pull ring. After cleaning the stopper with a pad soaked in sporicidal solution followed by pad soaked in alcohol, puncture the stopper with the needle.
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 after 24 hours. When convenient, smaller bottles can also be used. Instructions from the manufacturer of the auto injector/ pump must be followed.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL 00637/0018 (270 mg I/ml glass+USB)
PL 00637/0019 (320 mg I/ml glass+USB)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 March 1993

10. DATE OF REVISION OF THE TEXT

November 2025

GE HealthCare

1209858 GBR