HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Certificate of a Pharmaceutical Product

This certificate conforms to the format recommended by the World Health Organisation

Exporting (certifying) country: **Ireland**

Importing (requesting) country: **Moldova**

1. Name and dosage form of product:

VISIPAQUE (iodixanol) Injection 320mgI/ml (polypropylene bottle) known in Ireland as Visipaque 320 mgI/ml Solution for Injection, polypropylene container

1.1 Active ingredient(s) and amount(s) per unit dose:

	320 mgI/ml
Iodixanol *	652 mg

* Calculated on anhydrous basis

1.2 Is this product licensed to be placed on the market for use in the exporting country?
Yes

1.3 Is this product actually on the market in the exporting country?
Yes

If the answer to 1.2 is 'yes', continue with section 2.A and omit section 2B;
If the answer to 1.2 is 'no', omit section 2A and continue with section 2B

2A.1 Number of product licence and date of issue:

PA0735/009/013 issued 19th September 1995

2A.2 Product licence holder (name and address):

GE Healthcare AS,
P.O. Box 4220 Nydalen,
NO-0401 Oslo,
Norway.

Digitally signed by Chirtoacă Iurie
Date: 2022.01.05 10:51:56 EET
Reason: MoldSign Signature
Location: Moldova

2A.3 Status of product licence holder: a, b or c: **c**

2A.3.1 For categories b and c, state the name and address of the manufacturer producing the dosage form:

GE Healthcare Ireland Limited,
IDA Business Park,
Carrigtohill,
Co Cork,
Ireland.

2A.4 Is the summary Basis of Approval appended?
N/A

2A5. Is attached, officially approved product information complete and consonant with the licence?
Yes

2A.6 Applicant for certificate, if different from licence holder (name and address):

2B.1 Applicant for certificate (name and address):

2B.2 Status of applicant:

2B.2.1 For categories b and c, state the name and address of the manufacturer producing the dosage form:

2B.3 Why is marketing authorisation lacking?

2B.4 Remarks:

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?
Yes

3.1 Periodicity of routine inspection (years):
Every 3 years

3.2 Has the manufacture of this type of dosage form been inspected?
Yes

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organisation?
Yes

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For official HPRA use only:

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product?
Yes

Address of certifying authority:
Health Products Regulatory Authority
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Ireland

Telephone no: 01-676-4971 **Fax no:** 01-676-4061

Name of authorised person:

HPRA CERTIFIED

Paulina Nulty
A person authorised in that behalf by the said Authority
Compliance Department
7th August 2020

N.B. The information contained in the certificate is a valid and true reflection of the latest available information pertaining to the product authorisation available at the time of issue.

Explanatory notes

1. This certificate
the pharmaceu
country. It is
information
2. Use, wh
not

ROINN GNOTHAI EACHTRACHA
DEPARTMENT OF FOREIGN AFFAIRS

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country: Pays/País:	**IRELAND**
This public document Le présent acte public / El presente documento público	
2. has been signed by a été signé par ha sido firmado por	Paulina Nulty
3. acting in the capacity of agissant en qualité de quien actúa en calidad de	Health Products Regulatory Authority
4. bears the seal / stamp of est revêtu du sceau / timbre de y está revestido del sello / timbre de	Health Products Regulatory Authority

Certified
Attesté / Certificado

5. at à / en	Dublin	**6. the** le / el día	17/09/2020
7. by par / por	Department of Foreign Affairs and Trade		
8. No sous no bajo el número	6065402020		
9. Seal / stamp: Sceau / timbre: Sello / timbre:	**10. Signature:** Signature: Firma:		

This Apostille only certifies the authenticity of the signature and the capacity of the person who has signed the public document, and, where appropriate, the identity of the seal or stamp which the public document bears. This Apostille does not certify the content of the document for which it was issued. To verify the issuance of this Apostille, see www.authentications.dfat.ie

Explanatory notes

1. This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
2. Use, whenever possible, International Nonproprietary Names (INNs) or national nonproprietary names.
3. The formula (complete composition) of the dosage form should be given on the certificate or be appended.
4. Details of quantitative composition are preferred but their provision is subject to the agreement of the product-licence holder.
5. When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.
6. Sections 2A and 2B are mutually exclusive.
7. Indicate, when applicable, if the licence is provisional, or the product has not yet been approved.
8. Specify whether the person responsible for placing the product on the market:
   a. manufactures the dosage form;
   b. packages and/or labels a dosage form manufactured by an independent company; or
   c. is involved in none of the above.
9. This information can only be provided with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the product licence. If the production site is changed, the licence has to be updated or it is no longer valid.
10. This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
11. This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC)
12. In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission has to be provided to the authority by the applicant.
13. Please indicate the reason that the applicant has provided for not requesting registration.
   a. the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;
   b. the product has been reformulated with a view to improving its stability under tropical conditions;
   c. the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;
   d. the product has been reformulated to meet a different maximum dosage limit for an active ingredient;
   e. any other reason, please specify.
14. Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.
15. The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological

products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

16. This section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

mg I/ml Solution for Injection, 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 injections are supplied ready to use as clear, colourless to pale yellow aqueous solutions.
The pH of the product is 6.8-7.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.
X-ray contrast medium for use in adults for cardioangiography, cerebral angiography (conventional), peripheral angiography, (conventional), urography, CT-enhancement and studies of the gastrointestinal tract, lumbar, thoracic and cervical myelography and for use in children for cardioangiography, urography, CT-enhancement and studies of the 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 ... 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)

[(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	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)] 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.

Indication/Investigation	Concentration	Volume
Use in body cavities		The dosage must be adjusted individually to allow optimal visualisation
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		

	320 mg I/ml	80 – 200 ml has been studied
	320 mg I/ml	10 – 200 ml has been studied
	320 mg I/ml	20 – 200 ml has been studied
	270/320 mg I/ml	5 ml/kg b.w. 10-240 ml has been studied
ectal 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 listed in section 6.1.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 minor. However, iodinated contrast media may provoke anaphylactoid reactions or other manifestations of hypersensitivity.

The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/ anaphylactoid reactions should always be considered. The majority of serious undesirable reactions occur within the first 30 minutes. Late onset (that is 1 hour or more after application) hypersensitivity reactions can occur. A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment, should a serious reaction occur. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.

The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and reduces the responsiveness of treatment of anaphylactoid reactions with adrenaline.
Asthmatic patients are at higher risk on concomitant beta blocker therapy (see section 4.5)
Patients should be observed for at least 30 minutes after administration of VISIPAQUE.

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.

Risk for thromboembolism:
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 guidewire 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. Advanced life support facilities should be readily available.

Care should be taken in patients with homocystinuria.

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 (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:
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 demyelination.

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: Intravascular contrast studies with iodinated contrast media can lead to acute alteration of renal function and have been associated with lactic acidosis in patients with impaired renal function receiving metformin. To prevent lactic acidosis, serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium.

1. Patients with eGFR equal or greater than 60 ml/min/1.73 m^2 (CKD 1 and 2) can continue to take metformin normally.
2. Patients with eGFR 30-59 ml/min/1.73 m^2 (CKD 3):

    1. Patients receiving intravenous contrast medium with eGRF equal or greater than 45 ml/min /1.73 m^2 can continue to take metformin normally
    2. In patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73 m^2 metformin should be discontinued 48 hours before contrast medium and should only be restarted 48 hours after contrast medium if renal function has not deteriorated.

3. In patients with eGFR less than 30 ml/min/1.73 m^2 (CKD 4 and 5) or with an intercurrent illness causing reduced liver function or hypoxia, metformin is contraindicated and 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.

function:
ed in patients with severe disturbance of both renal and hepatic function as they may have significantly
dium clearance. Patients on haemodialysis may receive contrast media for radiological procedures.
time of contrast media injection with the haemodialysis session is unnecessary because there is no evidence
alysis protects patients with impaired renal function from contrast medium induced nephropathy.

ienia gravis:
dministration 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 at risk of thyrotoxicosis should be carefully evaluated before any use of iodinated contrast medium. Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goitre may be at risk of developing hyperthyroidism following injection of iodinated contrast media.
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.

Paediatric population:
One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media. Thyroid function should be checked in neonates during the first week of life, following administration of iodinated contrast agents to the mother during pregnancy. Repeat testing of thyroid function is recommended at 2 to 6 weeks of age, particularly in low birth weight newborn or premature newborn.
See also section 4.6.

Extravasation:
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.

Visipaque may, dependent on the indication, contain more than 23 mg sodium per dose. This must be taken into consideration in patients on a controlled sodium diet.

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.

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 interactions

All iodinated contrast media may affect the iodine binding capacity of the thyroid which may be reduced for up to several weeks, thus tests that measure iodine uptake (using radioactive iodine) will be affected.

High concentrations of contrast media in serum and urine can interfere with laboratory tests for bilirubin substances (e.g. iron, copper, calcium and phosphate). These substances should therefore not be assayed on examination.

Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate la 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 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).

Asthmatic patients are at higher risk on concomitant beta blocker therapy (see section 4.4).

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.

Thyroid function should be checked in neonates during the first week of life, following administration of iodinated contrast agents to the mother during pregnancy.

Repeat testing of thyroid function is recommended at 2 to 6 weeks of age, particularly in low birth weight newborn or premature newborn.

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.

Fertility:

The effect of VISIPAQUE on human reproduction has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction.

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 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.

Undesirable effects associated with VISIPAQUE are usually mild to moderate and transient in nature. Serious reactions as well s fatalities are only seen on very rare occasions, these may include acute-on-chronic renal failure, acute renal failure, naphylactic or anaphylactoid shock, hypersensitivity reaction followed by cardiac reactions (Kounis' syndrome), cardiac or ardio-respiratory arrest and myocardial infarction. Cardiac reaction may be promoted by the underlying disease or the rocedure.

lypersensitivity reactions may present as respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus, evere skin reactions, angioneurotic oedema, hypotension, fever, laryngeal oedema, bronchospasm or pulmonary oedema. In atients with autoimmune diseases cases of vasculitis and SJS-like syndrome were observed.

hey may appear either immediately after the injection or up to a few days later.

occur irrespectively of the dose and mode of administration and mild symptoms may represent naphylactoid reaction/shock.

e contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the atients using beta blockers may present with atypical symptoms of hypersensitivity which may be d as a vagal reaction.

ansient increase in serum creatinine is common after iodinated contrast media, but is usually of no clinical relevance.

e 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.

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: 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 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 patients with a rise of ≥ 1.0 mg/dl. 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.

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.
No specific pharmacokinetic studies have been performed for use in body cavities.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium chloride
Calcium chloride dihydrate
Sodium calcium edetate
Hydrochloric acid (pH adjustment)
Water for injections.

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

3 years.
The product must be used immediately after opening.

6.4 Special precautions for storage

Do not store above 30°C. Keep the container in the outer carton. Protect from secondary X-rays. The product in 50, 100, 200 and 500 ml polypropylene bottles can be stored for up to 1 month at 37°C. The product in 20 ml polypropylene bottles can be stored for up to 1 week at 37°C prior to use.

6.5 Nature and contents of container

The product is filled in polypropylene bottles. 20 and 50 ml bottles are rigid stand-up bottles with a twist-off top. Bottles of 50, 100, 200 and 500 ml are closed with chlorobutyl rubber stoppers (Ph. Eur. Type I), and supplied with a plastic screw cap which is provided with a tamper proof ring.

The product is supplied as:
Rigid stand-up bottles with twist-off top:

Bottle size	Pack size/Fill volume
20 ml	1 bottle of 10 ml, 10 bottles of 10 ml
	1 bottle of 20 ml, 10 bottles of 20 ml
50 ml	1 bottle of 40 ml, 10 bottles of 40 ml
	1 bottle of 50 ml, 10 bottles of 50 ml

Bottles with rubber stoppers and plastic screw cap:

Bottle size	Pack size/Fill volume
50 ml	1 bottle of 50 ml, 10 bottles of 50 ml
100 ml	1 bottle of 75 ml, 10 bottles of 75 ml
	1 bottle of 100 ml, 10 bottles of 100 ml
200 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
500 ml	1 bottle of 500 ml, 6 bottles of 500 ml

Not all pack sizes may be marketed.

posal of a used medicinal product or waste materials derived from such medicinal g of the product

iscard any unused contents.

eral products, VISIPAQUE should be inspected visually for particulate matter, discolouration and the integrity of ner prior to use.

e product should be drawn into the syringe immediately before use. VISIPAQUE may be warmed to body temperature before administration.

Additional instructions 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

GE Healthcare AS
P.O. Box 4220 Nydalen
NO-0401 Oslo
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8 MARKETING AUTHORISATION NUMBER

PA0735/009/013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 19 September 2010

10 DATE OF REVISION OF THE TEXT

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