

VISIPAQUE Solution for Injection - X-ray contrast medium

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Visipaque 270 mg I/ml and 320 mg I/ml Solution for Injection

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 ₂ O | 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.

For a 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.

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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 |
|-------------------------------------|--------------------------------|--|
| <u>Intra-arterial use</u> | | |
| Arteriographies | | |
| <u>Adults</u> | | |
| 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 | | |
| <u>Adults</u> | | |
| 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. |
| <u>Children</u> | | |
| | 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.

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| Indication/Investigation | Concentration | Volume |
|--|-------------------------------|---|
| <u>Intravenous use</u> | | |
| Urography | | |
| <u>Adults</u> | 270/320 mg I/ml | 40 – 80 ml ⁽²⁾ |
| <u>Children</u> < 7 kg | 270/320 mg I/ml | 2 – 4 ml/kg |
| <u>Children</u> > 7 kg | 270/320 mg I/ml | 2 – 3 ml/kg |
| All doses depending on age, weight and pathology (max. 50 ml). | | |
| Venography | | |
| <u>Adults</u> | 270 mg I/ml | 50 - 150 ml/leg |
| CT-enhancement | | |
| <u>Adults</u> | | |
| CT of the head | 270/320 mg I/ml | 50 – 150 ml |
| CT of the body | 270/320 mg I/ml | 75 – 150 ml |
| <u>Children</u> | | |
| 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) |
| <u>Intrathecal use</u> | | |
| 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⁾ |

⁽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.

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| Indication/Investigation | Concentration | Volume |
|--|-----------------|---|
| <u>Use in body cavities</u> | | |
| <u>Adults</u> | | |
| 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 <u>40 ml</u> has been studied). |
| <u>Gastrointestinal studies</u> | | |
| Oral use | | |
| <u>Adults</u> | | |
| 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 |
| <u>Children</u> | 320 mg I/ml | 5 ml/kg b.w. 10-240 ml has been studied |
| Rectal use | | |
| <u>Children</u> | 270/320 mg I/ml | 30 – 400 ml has been studied |

For elderly patients, patients with hepatic and/or renal impairment, 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:

A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H1 and H2 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.

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Non-ionic contrast media have less effect on the coagulation system in vitro, compared to ionic contrast media. When performing vascular catheterization procedures one should pay meticulous attention to the angiographic technique and flush the catheter frequently (e.g.: with heparinised saline) so as to 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.

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 reduce the risk of lactic acidosis, the serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast media and the following precautions undertaken in the following circumstances.

Normal serum creatinine (<130µmol/litre)/normal renal function: Administration of metformin should be stopped at the time of administration of contrast medium and not resumed for 48 hours unless renal function/serum creatinine remains in the normal range.

Abnormal serum creatinine (>130µmol/litre)/impaired renal function: Metformin should be stopped and the contrast medium examination delayed for 48 hours. Metformin should only be restarted if renal function is not diminished (if serum creatinine is not increased) compared to pre-contrast values.

Emergency cases: 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

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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.

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.

The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis. In patients with pheochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis. Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goiter may be at risk of developing hyperthyroidism following injection of iodinated contrast media. One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media.

Extravasation of Visipaque has not been reported, but it is likely that Visipaque due to its isotonicity gives rise to less local pain and extravascular oedema than hyperosmolar contrast media. In case of extravasation, elevating and cooling the affected site is recommended as routine measures. Surgical decompression may be necessary in cases of compartment syndrome.

Observation time

Patients must be kept under close observation for 15 minutes following the last injection as the majority of severe reactions occur at this time. 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 6 hours if remaining in bed. Patients suspected of having a low seizure threshold should be observed during this period. Outpatients should not be completely alone for the first 24 hours.

4.5 Interaction with other 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 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.

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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 previous to an iodinated contrast medium injection have been associated with an increased risk for delayed reactions (flu-like symptoms or skin reactions).

4.6 Pregnancy and lactation

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

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

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 for 6 hours following intrathecal procedure (see section 4.4).

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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. Hypersensitivity reactions may present as respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus, skin reactions including severe bullous or pustular 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

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The listed frequencies are based on internal clinical documentation and published studies, comprising more than 48,000 patients.

Intravascular administration:

Immune system disorders:

Uncommon: Hypersensitivity

Not known: Anaphylactoid reaction, anaphylactoid shock; severe pustular or bullous skin reactions

Psychiatric disorders:

Not known: Confusional state

Nervous system disorders:

Uncommon: Headache

Rare: Dizziness

Very rare: Sensory disturbance

Not known: Motor dysfunction, disturbance in consciousness, convulsion

Eye disorders:

Very rare: Blindness transient

Cardiac disorders:

Rare: Arrhythmia

Not known: Ventricular hypokinesia, myocardial ischaemia

Vascular disorders:

Rare: Hypotension

Very rare: Hypertension, ischaemia

Not known: Arterial spasm, thrombosis, thrombophlebitis

Respiratory, thoracic and mediastinal disorders:

Rare: Cough

Very rare: Dyspnoea

Not known: Non-cardiogenic pulmonary oedema

Gastrointestinal disorders:

Uncommon: Nausea, vomiting

Very rare: Abdominal pain/discomfort

Musculoskeletal and connective tissue disorders:

Not known: Arthralgia

Renal and urinary disorders:

Very rare: Acute renal failure

General disorders and administration site conditions:

Uncommon: Feeling hot

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

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

Injury, poisoning and procedural complications:

Not known: Iodism

Intrathecal administration:

Undesirable effects following intrathecal use may be delayed and present some hours or even days after the procedure. The frequency is similar to lumbar puncture alone.

Meningeal irritation giving photophobia and meningism and frank chemical meningitis have been observed with other non-ionic contrast media. The possibility of an infective meningitis should also be considered. Similarly, manifestations of transient cerebral dysfunction have been seen on very rare occasions with other non-ionic iodinate contrast media. These include seizures, transient confusion or transient motor or sensory dysfunction. Changes in the EEG were noted in a few of the patients.

Immune system disorders:

Not known: Hypersensitivity

Nervous system disorders:

Uncommon: Headache (may be severe and lasting)

Not known: Dizziness

Gastrointestinal disorders:

Uncommon: Vomiting

Not known: Nausea

General disorders and administration site conditions:

Not known: Shivering, pain at injection site

Hysterosalpingography (HSG):

Immune system disorders:

Not known: Hypersensitivity

Nervous system disorders:

Common: Headache

Gastrointestinal disorders:

Very common: Abdominal pain

Common: Nausea

Not known: Vomiting

Reproductive system and breast disorders:

Very common: Vaginal haemorrhage

General disorders and administration site conditions:

Common: Pyrexia

Not known: Shivering, injection site reaction

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Arthrography:

Immune system disorders:

Not known: Hypersensitivity

General disorders and administration site conditions:

Common: Injection site pain

Not known: Shivering

Examination of the GI tract:

Immune system disorders:

Not known: Hypersensitivity

Gastrointestinal disorders:

Common: Diarrhoea, abdominal pain, nausea

Uncommon: Vomiting

General disorders and administration site reaction

Not known: Shivering

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 ($t_{1/2} \sim 2$ hours). In the event of accidental overdosing, the water and electrolyte losses must be compensated by infusion. Renal function should be monitored for at least the next 3 days. If needed, haemodialysis may be used to remove iodixanol from the patient's system. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: X-ray contrast medium, iodinated

ATC code: 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 $\mu\text{mol/L}$, Visipaque use resulted in 3% of patients experiencing a rise in creatinine of $\geq 44.2 \mu\text{mol/L}$ and 0% of the patients with a rise of $\geq 88.4 \mu\text{mol/L}$. The release of enzymes (alkaline phosphatase and N-acetyl- β -glucosaminidase) from the

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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 ($t_{1/2}$ approx. 4 hours in newborns). 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 has 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,
sodium calcium edetate,
hydrochloric acid (pH adjustment) and
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.

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6.3 Shelf life

The shelf life is 3 years.

6.4 Special precautions for storage

Keep the container in the outer carton. The product in glass containers 40, 50, 75, 100, 150, 175 and 200 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 vials/bottles:

The product is filled in injection vials (20 ml) and infusion bottles (50, 75, 100 and 200 ml). The glass vials/bottles are made of colourless highly resistant borosilicate glass (Ph. Eur. Type I), closed with black chlorobutyl rubber stoppers (Ph. Eur. Type I), and sealed with complete tear off caps with coloured plastic "flip-off" tops.

Polypropylene bottles:

The product is filled in polypropylene bottles. The bottles of 50, 75, 100, 150, 175 and 200 ml are closed with chlorobutyl rubber stoppers (Ph.Eur. Type I) and supplied with a screw cap which is provided with a tamper proof ring.

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The product is supplied as:

270 mg I/ml:

| | |
|-----------------------------------|------------------------------------|
| 10 vials of 20 ml | 1 polypropylene bottle of 75 ml |
| 10 bottles of 50 ml | 10 polypropylene bottles of 75 ml |
| 10 bottles of 75 ml | 1 polypropylene bottle of 100 ml |
| 1 bottle of 100 ml | 10 polypropylene bottles of 100 ml |
| 10 bottles of 100 ml | 1 polypropylene bottle of 150 ml |
| 1 bottle of 200 ml | 10 polypropylene bottles of 150 ml |
| 6 bottles of 200 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 |
| 1 polypropylene bottle of 50 ml | |
| 10 polypropylene bottles of 50 ml | |

320 mg I/ml:

| | |
|-----------------------------------|------------------------------------|
| 10 vials of 20 ml | 1 polypropylene bottle of 75 ml |
| 10 bottles of 50 ml | 10 polypropylene bottles of 75 ml |
| 1 bottle of 100 ml | 1 polypropylene bottle of 100 ml |
| 10 bottles of 100 ml | 10 polypropylene bottles of 100 ml |
| 1 bottle of 200 ml | 1 polypropylene bottle of 150 ml |
| 6 bottles of 200 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 |
| 1 polypropylene bottle of 50 ml | |
| 10 polypropylene bottles of 50 ml | |

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.

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

7. MARKETING AUTHORIZATION 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

26 July 2006 (Company name change)
8 October 2007 (New safety according to CCSI)
30 May 2008 (SPC update section 4.8)
26 April 2010 (New safety according to CCSI)