SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Omnipaque Injection 350mg I/ml solution for injection

2. QUALITATIVE AND QUANTITATIV COMPOSITION

Active ingredient	Strength	Content per ml
Iohexol (INN)	140 mg I/ml	302 mg equiv. 140 mg I
Iohexol (INN)	240 mg I/ml	518 mg equiv. 240 mg I
Iohexol (INN)	300 mg I/ml	647 mg equiv. 300 mg I
Iohexol (INN)	350 mg I/ml	755 mg equiv. 350 mg I

For a full list of excipients, see section 6.1.

Iohexol is a non-ionic, monomeric, triiodinated, water-soluble X-ray contrast medium. Omnipaque in the concentration of 140 mg I/ml is isotonic with blood and tissue fluid.
The osmolality and viscosity values of Omnipaque are as follows:

Concentration	Osmolality * mOsm/kg H_2O	Viscosity (mPa·s)*	
	37°C	20°C	37°C
140 mg I/ml	290	2.3	1.5
240 mg I/ml	510	5.6	3.3
300 mg I/ml	640	11.6	6.1
350 mg I/ml	780	23.3	10.6

* in aqueous solution of iohexol

3. PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

X-ray contrast medium for use in adults and children for urography, phlebography, i.v. DSA, CT, arteriography, cardioangiography and i.a. DSA. Myelography. For use in body cavities: Arthrography, ERP/ERCP, herniography, hysterosalpingography, sialography and use in the G-I tract. Contrast-enhanced mammography (CEM) in adults to evaluate and detect known or suspected lesions of the breast, as an adjunct to mammography (with or without ultrasound) or as an alternative to magnetic resonance imaging (MRI) when MRI is contraindicated or unavailable.

4.2 Posology and method of administration

The dosage depends on the type of investigation and the technique used. Usually the same iodine concentration and volume is used as for other iodinated X-ray contrast media in current use.
Adequate hydration should be assured before and after administration as for other contrast media.

For intravenous, intra-arterial and intrathecal use, and use in body cavities.

The following dosages may serve as a guide:

Guidelines for intravenous use

Indication	Concentration	Volume	Comments
Urography Adults Children < 7 kg Children > 7 kg	 300 mg I/ml or 350 mg I/ml 240 mg I/ml or 300 mg I/ml 240 mg I/ml or 300 mg I/ml	 40-80 ml 40-80 ml 4 ml/kg b.w. 3 ml/kg b.w. 3 ml/kg b.w. 2 ml/kg b.w.	
Phlebography (leg)	240 mg I/ml or 300 mg I/ml	20-100 ml/leg	
Digital subtraction angiography Adults Children	140 mg I/ml 300 mg I/ml or 350 mg I/ml 140 mg I/ml	Up to 3 ml per kg body weight 20 - 60 ml/inj. 20 - 60 ml/inj. dependent upon age, weight and pathology	

Contrast-enhanced mammography (CEM)	300 mg I/ml or 350 mg I/ml	**Dose (per kg body weight)** 1.5 mL/kg b.w. 1.3 mL/kg b.w.	
CT enhancement <u>Adults</u>	140 mg I/ml or 240 mg I/ml or 300 mg I/ml or 350 mg I/ml	100-400 ml 100-250 ml 100-200 ml 100-150 ml	

<u>Guidelines for intra-arterial use</u>

Indication	Concentration	Volume	Comments
Arteriographies Arch aortography	300 mg I/ml	30-40 ml/inj.	
Selective cerebral	300 mg I/ml	5-10 ml/inj.	
Aortography	350 mg I/ml	40-60 ml/inj.	
Femoral	300 mg I/ml or 350 mg I/ml	30-50 ml/inj.	
Various	300 mg I/ml	depending on type of examination	
Cardioangiography <u>Adults</u> Left ventricle and aortic root inj.	350 mg I/ml	30-60 ml/inj.	
Selective coronary arteriography	350 mg I/ml	4-8 ml/inj.	
<u>Children</u>	300 mg I/ml or 350 mg I/ml	depending on age, weight and pathology (max 8 ml/kg b.w.)	
Digital subtraction angiography <u>Adults</u>	140 mg I/ml or 240 mg I/ml or 300 mg I/ml	4 - 10 ml/inj. 1 - 15 ml/inj. 1 - 15 ml/inj.	
<u>Children</u>	140 mg I/ml	Dependent upon age, weight and pathology	

Guidelines for intrathecal use

Indication	Concentration	Volume	Comments
Lumbar and thoracic myelography (lumbar injection)	240 mg I/ml	8 - 12 ml	
Cervical myelography (lumbar injection)	240 mg I/ml or 300 mg I/ml	10-12 ml 7 - 10 ml	
Cervical myelography (lateral cervical injection)	240 mg I/ml or 300 mg I/ml	6 - 10 ml 6 - 8 ml	
CT cisternography (lumbar injection)	240 mg I/ml	4 - 12 ml	

To minimize possible adverse reactions a total dose of 3 g iodine should not be exceeded.

Guidelines for body cavities

Indication	Concentration	Volume	Comments
Arthrography	240 mg I/ml or 300 mg I/ml or 350 mg I/ml	5 - 20 ml 5 - 15 ml 5 - 10 ml	
ERP/ERCP	240 mg I/ml	20 - 50 ml	
Herniography	240 mg I/ml	50 ml	
Hysterosalpingography	240 mg I/ml or 300 mg I/ml	15 - 50 ml 15 - 25 ml	
Sialography	240 mg I/ml or 300 mg I/ml	0.5 - 2 ml 0.5 - 2 ml	
Gastrointestinal studies	350 mg I/ml	10-20ml	

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 monomeric contrast media in general:

Hypersensitivity: A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Any application of contrast media should, therefore, be preceded by a detailed medical history, in patients with allergic diathesis and in patients with known hypersensitivity reactions a very strict indication is required.

In patients with an increased risk of acute hypersensitivity reactions, a previous moderate or severe acute reaction to contrast agent, asthma or allergy requiring medical treatment, premedication with corticosteroids or antihistamines may be considered. However, premedication does not prevent severe reactions but may reduce their incidence and severity. In patients with bronchial asthma especially the risk for bronchospasm is increased.

The risk of serious reactions in connection with use of Omnipaque is regarded as minor. However, iodinated contrast media may provoke serious, life-threatening, fatal anaphylactic/anaphylactoid reactions or other manifestations of hypersensitivity.

Independent of quantity and route of administration, symptoms such as angio-oedema, conjunctivitis, coughing, pruritus, rhinitis, sneezing and urticaria may be indicative of a serious anaphylactoid reaction requiring treatment.

A course of action should therefore be planned in advance, with necessary drugs and equipment, medical experience and skilled personnel available for immediate treatment, should a serious reaction occur. In imminent state of shock, administration of the contrast medium must be terminated immediately and - if necessary - specific intravenous treatment must be initiated. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.

Patients using beta-adrenergic blocking agents, particularly asthmatic patients, may have a lower threshold for bronchospasm and are less responsive to treatment with beta agonists and adrenaline, which may necessitate the use of higher doses.

Usually, hypersensitivity reactions become manifest as minor respiratory or cutaneous symptoms, such as mild difficulties of breathing, skin reddening (erythema), urticaria, pruritus or facial oedema. Severe reactions such as angio-oedema, subglottis oedema, bronchial spasm and shock are rare.

These reactions usually occur within one hour following application of the contrast medium. In rare cases, hypersensitivity may occur delayed (after hours or days), but these cases are rarely life threatening, and mainly affect the skin.

Hydration:

Adequate hydration should be assured before and after contrast media administration. If necessary, the patient should be hydrated intravenously until excretion of the contrast medium is complete. This applies especially to patients with dys- and paraproteinaemias like multiple myeloma, diabetes mellitus, renal dysfunction, hyperuricaemia, as well as to infants, small children, elderly patients and patients in bad general condition. In patients at risk the water and electrolyte metabolism must be controlled and symptoms of a dropping serum calcium level must be taken care of. Due to the risk of dehydration induced by diuretics, at first, water and electrolyte rehydration is necessary to limit the risk of acute renal failure.

Cardio-circulatory reactions:

Care should also be taken in patients with serious cardiac disease /cardio-circulatory disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias.

This is especially applicable following intracoronary, left and right ventricular application of contrast media (see also section 4.8).

Patients with cardiac insufficiency, severe coronary heart disease, instable angina pectoris, valvular diseases, previous myocardial infarction, coronary bypass and pulmonary hypertension are especially predisposed for cardiac reactions.

In elderly patients and patients with pre-existing cardiac diseases reactions with ischemic changes in the ECG and arrhythmia occur more frequently.

In patients with cardiac insufficiency intravasal injection of contrast media can induce pulmonary oedema.

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.

Encephalopathy has been reported with the use of contrast media, such as iohexol. Contrast encephalopathy may manifest with symptoms and signs of neurological dysfunction (see “Description of selected adverse reactions” section 4.8). Symptoms usually occur within minutes to hours after administration of iohexol, and generally resolve within days.

Factors which increase blood-brain barrier permeability will ease the transfer of contrast media to brain tissue and may lead to possible CNS reactions for instance encephalopathy.

Caution is advised in intravascular application to patients with acute cerebral infarction or acute intracranial bleeding as well as in patients with diseases causing disturbance of the blood-brain barrier, and in patients with brain oedema, acute demyelinisation or advanced cerebral atherosclerosis.

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

Neurological symptoms caused by metastases, degenerative or inflammatory processes can be aggravated by application of contrast media.

Patients with symptomatic cerebrovascular diseases, previous stroke or frequent transitory ischemic attacks are at increased risk for contrast medium-induced neurological complications following intra-arterial injection. Intra-arterial injection of contrast media may induce vasospasm with resulting cerebral ischaemic phenomena.

A few patients have experienced a temporary hearing loss or even deafness after myelography, which is believed to be due to a drop in spinal fluid pressure by the lumbar puncture per se.

Renal reactions:

Use of iodinated contrast media may cause contrast induced nephropathy, impairment of renal function or acute renal failure. To prevent these conditions following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk.

Other predisposing factors are preceding renal failure following application of contrast media, a history of renal disease, age over 60 years, dehydration, advanced arteriosclerosis, decompensated cardiac insufficiency, high doses of contrast media and multiple injections, direct application of contrast media to the renal artery, exposition to further nephrotoxins, severe and chronic hypertension, hyperuricaeia, paraproteinemias (myelomatosis and Waldenström's macroglobulinemia, plasmocytoma) or dysproteinemias.

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 reduction to a minimum.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

Patients on haemodialysis may receive contrast media for radiological procedures. Correlation of the time of contrast media injection with the haemodialysis session is unnecessary.

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:

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

(2) Patients with eGFR 30-59 ml/min/1.73m^2 (CKD 3)

- Patients receiving intravenous contrast medium with eGFR equal or greater than 45 ml/min /1.73m^2) 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/1.73m^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/1.73m^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. It is particularly important that the patient is 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, as well as the patient with regard to signs of lactic acidosis.

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. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

Patients with disturbance of both hepatic and renal 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.

Disturbed thyroid function:

Due to free iodide in the solutions and additional iodide released by deiodination, iodinated contrast media influence thyroid function. This may induce hyperthyroidism or even thyrotoxic crisis in predisposed patients.

Patients with manifest but not yet diagnosed hyperthyroidism are at risk, patients with latent hyperthyroidism (e.g., nodular goitre) and patients with functional autonomy (often e.g. elderly patients, especially in regions with iodine deficiency) should therefore have their thyroid function assessed before examination if such conditions are suspected.

Before administering an iodinated contrast agent, make sure that the patient is not about to undergo thyroid scan or thyroid function tests or treatment with radioactive iodine, as administration of iodinated contrast agents, regardless of the route, interferes with hormone assays and iodine uptake by the thyroid gland or metastases from thyroid cancer until urinary iodine excretion returns to normal. See also section 4.5.

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. See also section on Paediatric population.

Anxiety conditions:

A sedative may be administered in the case of marked anxiety.

Sickle cell disease:

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when injected intravenously and intra-arterially.

Further risk factors:

Among patients with autoimmune diseases cases of serious vasculitis or Stevens Johnson-like syndromes have been observed.

Severe vascular and neurological diseases, especially in elderly patients are risk factors for reactions to contrast media.

Extravasation:

Extravasation of contrast media may on rare occasions give rise to local pain, and oedema and erythema, which usually recedes without sequelae. However, inflammation and even tissue necrosis have been seen. 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 30 minutes following the last injection as the majority of severe reactions occur at this time.

Coagulopathy

Catheter angiography with contrast media carries a risk to induce thromboembolic events. *In vitro*, non-ionic contrast media have a weaker coagulation inhibiting effect than ionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiocardiographic procedures with both ionic and non-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 heparinized saline) so as to minimize the risk of procedure-related thrombosis and embolism. The examination shall be kept as short as possible. Care should be taken in patients with homocystinuria. (Risk for thromboembolism).

During catheterization it should be considered that besides the contrast medium numerous other factors may also influence the development of thromboembolic events.

These are: duration of the examination, number of injections, type of catheter and syringe material, existing underlying diseases and concomitant medication.

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.

Cerebral arteriography

In patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, old age, and previous cerebral thrombosis or embolism and migraine, cardiovascular reactions such as bradycardia and increases or decreases in blood pressure may occur more often.

Arteriography

In relation to procedure used, injury of the artery, vein, aorta and adjacent organs, pleurocentesis, retroperitoneal bleeding, spinal cord injury and symptoms of paraplegia may occur.

Paediatric population:

Hypothyroidism or transient thyroid suppression may be observed after exposure to iodinated contrast media. 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 within 3 weeks following exposure to iodinated contrast media, especially in premature infants and neonates. If hypothyroidism is detected, thyroid function should be monitored as appropriate even when replacement treatment is given.

Especially in infants and small children, adequate hydration should be assured before and after contrast media administration. Nephrotoxic medication should be suspended. The age dependent reduced glomerular filtration rate in infants can also result in delayed excretion of contrast agents.

Young infants (age < 1 year) and especially neonates are susceptible to electrolyte disturbance and haemodynamic alterations.

Contrast-enhanced mammography (CEM)

Contrast-enhanced mammography results in higher patient exposure to ionizing radiation than standard mammography. Radiation dose depends on breast thickness, the type of mammographic device and the device's system settings. The overall CEM radiation dose remains under the threshold defined by international guidelines for mammography (below 3 mGy).

4.5 Interaction with other medicinal products and other forms of interaction

Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking metformin (see section 4.4).

Patients treated with interleukin-2 and interferons less than two weeks previously have been associated with an increased risk for delayed reactions (erythema, flu-like symptoms or skin reactions).

The concomitant use of certain neuroleptics or tricyclic antidepressants can reduce the seizure threshold and thus increase the risk of contrast medium-induced seizures.

Treatment with β-blockers may lower the threshold for hypersensitivity reactions, as well as necessitating higher doses of β-agonists when treating hypersensitivity reactions.

Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists may reduce efficacy of cardiovascular compensation mechanisms of blood pressure changes.

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.

4.6 Fertility, pregnancy and lactation

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

Apart from avoidance of exposition to radiation, the sensitivity of the foetal thyroid gland to iodine should be taken into account when risk and benefit are evaluated..

Thyroid function should be checked in all 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. The amount of iohexol in breast milk excreted in 24 hours after injection was 0.5% of the weight adjusted dose in a trial. The amount of iohexol ingested by the baby in the first 24 hours after injection corresponds to only 0.2% of the paediatric dose.

4.7 Effects on ability to drive and use machines

It is not advisable to drive a car or use machines for one hour after the last injection or for 24 hours following intrathecal procedure (see section 4.4). However, individual judgement must be performed if persistent post myelography symptoms.

4.8 Undesirable effects

The listed frequencies are based on internal clinical documentation and published large scale studies, comprising more than 200,000 patients.

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)

General (applies to all uses of iodinated contrast media)
Below are listed possible general side effects in relation with radiographic procedures, which include the use of non-ionic monomeric contrast media. For side effects specific to mode of administration, please refer to these specific sections.

Hypersensitivity reactions may occur irrespective 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.

A transient increase in S-creatinine is common after iodinated contrast media, contrast induced nephropathy may occur.

Iodism or “iodide mumps” is a very rare complication of iodinated contrast media resulting in swelling and tenderness of the salivary glands for up to approximately 10 days after the examination.

Immune system disorders:
Rare: Hypersensitivity (may be life-threatening or fatal) (including dyspnoea, rash, erythema, urticaria, pruritus, skin reaction, conjunctivitis, coughing, rhinitis, sneezing, vasculitis, angioneurotic oedema, laryngeal oedema, laryngospasm, bronchospasm or non-cardiogenic pulmonary oedema). They may appear either immediately after the injection or up to a few days later and may be indicative of the beginning of a state of shock. Hypersensitivity related skin reactions may appear up to a few days after the injection.

Very rare: Anaphylactic/anaphylactoid reaction (may be life-threatening or fatal)
Not known: Anaphylactic/anaphylactoid shock (may be life-threatening or fatal)

Nervous system disorders:
Uncommon: Headache
Very rare: Dysgeusia (transient metallic taste), syncope vasovagal

Cardiac disorders:
Rare: Bradycardia

Vascular disorders:
Very rare: Hypertension, hypotension

Gastrointestinal disorders:
Uncommon: Nausea
Rare: Vomiting, abdominal pain
Very rare: Diarrhoea
Not known: Salivary gland enlargement

General disorders and administration site conditions:
Common: Feeling hot
Uncommon: Hyperhidrosis, cold feeling, vasovagal reactions
Rare: Pyrexia
Very rare: Shivering (chills)

Intravascular use (Intraarterial and Intravenous use)
Please first read the section labelled "General". Below, only undesirable events with frequency during intravascular use of nonionic monomeric contrast media are described. The nature of the undesirable effects specifically seen during intraarterial use depends on the site of injection and dose given. Selective arteriographies and other procedures in which the contrast medium reaches a particular organ in high concentrations may be accompanied by complications in that particular organ.

Blood and lymphatic system disorders:
Not known: Thrombocytopenia

Endocrine disorders:
Not known: Thyrotoxicosis**,** transient hypothyroidism

Psychiatric disorders:
Not known: Confusion, agitation, restlessness, anxiety, disorientation

Nervous system disorders:
Rare: Dizziness, paresis, paralysis, somnolence
Very rare: Seizures, disturbance in consciousness, cerebrovascular accident, stupor, sensory abnormalities (including hypoaesthesia), paraesthesia, tremor.
Not known: Amnesia, transient motor dysfunction (including speech disorder, aphasia, dysarthria), contrast encephalopathy (see “Description of selected adverse reactions” in section 4.8).

Eye disorders:
Rare: Visual impairment (including diplopia and blurred vision), photophobia
Not known: Transient cortical blindness

Ear and labyrinth disorders:
Not known: Transient hearing loss

Cardiac disorders:
Rare: Arrhythmia (including bradycardia, tachycardia).

Very rare: myocardial infarction, chest pain
Not known: Severe cardiac complications (including cardiac arrest**,** cardio-respiratory arrest), cardiac failure, spasm of coronary arteries, cyanosis

Vascular disorders:
Very rare: Flushing
Not known: Shock, arterial spasm, thrombophlebitis and venous thrombosis

Respiratory, thoracic and mediastinal disorders:
Common: Transient changes in respiratory rate, respiratory distress
Rare: Cough, respiratory arrest
Very rare: Dyspnoea
Not known: Severe respiratory symptoms and signs**,** pulmonary oedema, acute respiratory distress syndrome, bronchospasm, laryngospasm, apnoea, aspiration, asthma attack

Gastrointestinal disorders:
Rare: Diarrhoea
Not known: Aggravation of pancreatitis

Skin and subcutaneous tissue disorders:
Rare: Rash, pruritus, urticaria
Not known: Angioedema, Bullous dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, psoriasis flare-up, erythema, drug eruption, skin exfoliation.

Musculoskeletal and connective tissue disorders:
Not known: Arthralgia, muscular weakness, musculoskeletal spasm, back pain

Renal and urinary system disorders:
Uncommon: Acute kidney injury
Not known: Blood creatinine increased

General disorders and administration site conditions:
Uncommon: Pain and discomfort
Rare: Asthenic conditions (including malaise, fatigue).
Not known: Administration site reactions, including extravasation

Injury, poisoning and procedural complications:
Not known: Iodism

Intrathecal use
Please first read the section labelled "General". Below, only undesirable events with frequency during intrathecal use of nonionic monomer contrast media are described. 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. Headache, nausea, vomiting or dizziness may largely be attributed to pressure loss in the sub-arachnoid space resulting from leakage at the puncture site. Excessive removal of cerebrospinal fluid should be avoided in order to minimise pressure loss.

Psychiatric disorders:
Not known: Confusion, agitation, anxiety, disorientation

Nervous system disorders:
Very common: Headache (may be severe and prolonged)
Uncommon: Aseptic meningitis (including chemical meningitis).
Rare: Seizures, dizziness
Not known: Meningism, status epilepticus, contrast encephalopathy (see "Description of selected adverse reactions" in section 4.8), motor dysfunction (including speech disorder, aphasia, dysarthria), paraesthesia, hypoesthesia and sensory disturbance

Eye disorders:
Not known: Transient cortical blindness, photophobia

Ear and labyrinth disorders:
Not known: Transient hearing loss

Gastrointestinal disorders:
Common: Nausea, vomiting

Musculoskeletal and connective tissue disorders÷
Rare: Neck pain, back pain
Not known: Muscle spasm

General disorders and administration site conditions:
Rare: Pain in extremity
Not known: Administration site conditions

Use in Body Cavities
Please first read the section labelled "General". Below, only undesirable events with frequency during use of non-ionic monomeric contrast media in body cavities are described.

Endoscopic Retrograde Cholangiopancreatography (ERCP):

Gastrointestinal disorders:
Common: Pancreatitis, blood amylase increased

Oral use:

Gastrointestinal disorders:

Very common: Diarrhoea
Common: Nausea, vomiting
Uncommon: Abdominal pain

Hysterosalpingography (HSG):

Gastrointestinal disorders:
Very common: Lower abdominal pain

Arthrography:

Musculoskeletal and connective tissue disorders:
Not known: Arthritis

General disorders and administration site
conditions: Very common: Pain

Herniography:

General disorders and administration site conditions:
Not known: Post procedural pain

Description of selected adverse reactions

Thrombo-embolic complications have been reported in connection with contrast-enhanced angiography of coronary, cerebral, renal and peripheral arteries. The contrast agent may have contributed to the complications (see section 4.4).

Cardiac complications including acute myocardial infarction have been reported during or after contrast-enhanced coronary angiography. Elderly patients or patients with severe coronary artery disease, unstable angina pectoris and left ventricular dysfunction had a higher risk (see section 4.4).

In very rare occasions the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex and cause contrast encephalopathy after intravascular or intrathecal administration (see section 4.4). The symptoms may include headache, visual disturbance, cortical blindness, seizures, confusion, disorientation, somnolence, loss of consciousness, coma, loss of coordination, hemiparesis, speech disorder, aphasia, amnesia, and brain oedema. Symptoms usually occur within few minutes to 24 hours after the administration. In majority of the case reports the reaction lasted few hours to up to 72 hours.

Anaphylactoid reaction and anaphylactoid shock may lead to profound hypotension and related symptoms and signs like hypoxic encephalopathy, renal and hepatic failure (see section 4.4).
In several cases, extravasation of contrast media has caused local pain and oedema, which usually receded without sequelae. Inflammation, tissue necrosis and compartment syndrome have occurred (see section 4.4).

Paediatric patients:

Transient hypothyroidism has been reported in premature infants, neonates and in other children after administration of iodinated contrast media. Premature infants are particularly sensitive to the effect of iodine. Transient hypothyroidism in a premature breast fed infant has been reported. The nursing mother was repeatedly exposed to Omnipaque (see section 4.4).
Especially in infants and small children, adequate hydration should be assured before and after contrast media administration. Nephrotoxic medication should be suspended. The age dependent reduced glomerular filtration rate in infants can also result in delayed excretion of contrast agents.

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 Yellow Card Scheme

Website: https://yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Preclinical data indicate a high safety margin for Omnipaque and no fixed upper dose level has been established for routine intravascular use. Symptomatic overdosing is unlikely in patients with normal renal function unless the patient has received an excess of 2000 mg I/kg body-weight over a limited period of time. The duration of the procedure is important for the renal tolerability of high doses of contrast media ($t_{½}$ ~ 2 hours). Accidental overdosing is most likely following complex angiographic procedures in children, particularly when multiple injections of contrast medium with high-concentration are given.

In cases of overdose, any resulting water- or electrolyte imbalance must be corrected. Renal function should be monitored for the next 3 days. If needed, haemodialysis may be used for clearance of excessive contrast medium. There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: X-ray contrast media, iodinated, ATC code: V08AB02

For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iohexol 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.

5.2 Pharmacokinetic properties

Close to 100 per cent of the intravenously injected iohexol is excreted unchanged through the kidneys within 24 hours in patients with normal renal function. The maximum urinary concentration of iohexol appears within approximately 1 hour after injection. No metabolites have been detected. The protein binding of Omnipaque is very low (less than 2 %).

5.3. Pre-clinical Safety Data

Iohexol has a very low acute intravenous toxicity in mice and rats. Animal studies have shown that iohexol has a very low protein binding, and is well tolerated by the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The following excipients are included:

Trometamol
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

Glass bottles:	3 years
Polypropylene bottles:	3 years

In-use shelf-life: Chemical and physical in-use stability for the iohexol solution in the 500, 700 and 1000 ml polypropylene bottles has been demonstrated for 24 hours at 25ºC.

The expiry date is indicated on the label.

6.4 Special precautions for storage

Store at or below 30 °C.

Store in the original package to protect from light.

The glass vials and bottles can be stored at 37°C for up to 3 months prior to use.
The polypropylene bottles can be stored at 37°C for up to 1 month prior to use.

6.5 Nature and contents of container

Glass bottles:
The product is filled in infusion vials (10, 15 and 20 ml) and infusion bottles (40, 50, 75, 100 and 200 ml). Both 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 combined "flip off seal/tear off seal - flat plast disc".

Polypropylene bottles:

The product is filled in polypropylene bottles. Bottles of 50, 75, 100, 150, 175, 200, 500, 700 and 1000 ml are closed with halobutyl rubber stoppers and sealed with a plastic screw cap, which is provided with a tamper proof ring

The product is supplied as:

Glass vials/bottles:

140 mg I/ml	240 mg I/ml	300 mg I/ml	350 mg I/ml
10 bottles of 50ml 6 bottles of 200ml	10 vials of 10ml 6 vials of 20ml 25 vials of 20ml 10 bottles of 50ml 6 bottles of 200ml	10 vials of 10ml 6 vials of 20ml 25 vials of 20ml 10 bottles of 50ml 10 bottles of 75ml 10 bottles of 100ml	6 vials of 20ml 25 vials of 20ml 10 bottles of 40ml 10 bottles of 50ml 10 bottles of 75ml 10 bottles of 100ml 6 bottles of 200ml

Polypropylene bottles:

140 mg I/ml	240 mg I/ml	300 mg I/ml	350 mg I/ml

10 bottles of 50 ml 1 bottle of 100ml 10 bottles of 100ml 1 bottle of 200ml 10 bottles of 200ml	10 bottles of 50 ml 1 bottle of 100ml 10 bottles of 100ml 1 bottle of 200ml 10 bottles of 200ml	10 bottles of 50ml 1 bottle of 75ml 10 bottles of 75ml 1 bottle of 100ml 10 bottles of 100ml 1 bottle of 150ml 10 bottles of 150ml 1 bottle of 175ml 10 bottles of 175ml 1 bottle of 200ml 10 bottles of 200ml 6 bottles of 500 ml 4 bottles of 700 ml 4 bottles of 1000 ml	10 bottles of 50ml 1 bottle of 75ml 10 bottles of 75ml 1 bottle of 100ml 10 bottles of 100ml 1 bottle of 150ml 10 bottles of 150ml 1 bottle of 175ml 10 bottles of 175ml 1 bottle of 200ml 10 bottles of 200ml 6 bottles of 500 ml 4 bottles of 700 ml 4 bottles of 1000 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Like all parenteral products, Omnipaque should be inspected visually for particulate matter, discolouration and the integrity of the container prior to use.

Omnipaque 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, 700 and 1000 ml

Chemical and physical in-use stability for the iohexol solution in the 500, 700 and 1000 ml polypropylene bottles has been demonstrated for 24 hours at 25˚C. 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 at temperatures below 25˚C, unless opening has taken place under controlled and validated aseptic conditions.

- The 500, 700 and 1000 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 a 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.

- Instructions from the manufacturer of the auto injector/pump must be followed.

7 MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

PL 00637/0036

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

23 November 1998

10 DATE OF REVISION OF THE TEXT

14/04/2026