SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

OMNIPAQUE 240 mg I/ml, 300 mg I/ml, 350 mg I/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	Strength	Content per ml
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.
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
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

X-ray contrast medium for use in adults and children for cardioangiography, arteriography, urography, phlebography and CT-enhancement. Lumbar, thoracic, cervical myelography and computed tomography of the basal cisterns, following subarachnoid injection. Arthrography, endoscopic retrograde pancreatography (ERP), endoscopic retrograde cholangiopancreatography (ERCP), herniography, hysterosalpingography, sialography and studies of the gastrointestinal tract.

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:	300 mg I/ml or 350 mg I/ml	40 - 80 ml 40 - 80 ml	80 ml may be exceeded in selected cases
children < 7 kg	240 mg I/ml or 300 mg I/ml	4 ml/kg b.w. 3 ml/kg b.w.	
children > 7 kg	240 mg I/ml or 300 mg I/ml	3 ml/kg b.w. 2 ml/kg b.w. (max 40 ml)	
Phlebography (leg)	240 mg I/ml or 300 mg I/ml	20 - 100 ml/leg	
Digital subtraction angiography	300 mg I/ml or 350 mg I/ml	20 - 60 ml/inj. 20 - 60 ml/inj.	
CT-enhancement adults:	240 mg I/ml or 300 mg I/ml or 350 mg I/ml	100 - 250 ml 100 - 200 ml 100 - 150 ml	Total amount of iodine usually 30 - 60 g
children:	240 mg I/ml or 300 mg I/ml	2-3 ml/kg b.w. up to 40 ml 1-3 ml/kg b.w. up to 40 ml	In a few cases up to 100 ml may be given

Guidelines for intra-arterial use

Indication	Concentration	Volume	Comments
Arteriographies			
arch aortography selective cerebral aortography femoral	300 mg I/ml 300 mg I/ml 350 mg I/ml 300 mg I/ml or 350 mg I/ml	30 - 40 ml/inj. 5 - 10 ml/inj. 40 - 60 ml/inj. 30 - 50 ml/inj.	Volume per injection depends on the site of injection
various	300 mg I/ml	depending on type of examination	

Indication	Concentration	Volume	Comments
Cardioangiography adults: left ventricle and aortic root inj. selective coronary arteriography children:	 350 mg I/ml 350 mg I/ml 300 mg I/ml or 350 mg I/ml	 30 - 60 ml/inj. 4 - 8 ml/inj. depending on age, weight and pathology (max 8 ml/kg b.w.)	
Digital subtraction angiography	240 mg I/ml or 300 mg I/ml	1 - 15 ml/inj. 1 - 15 ml/inj.	depending on site of inj. occasionally large volumes - up to 30 ml - may be used

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	300 mg I/ml or 350 mg I/ml	5 - 15 ml 5 - 10 ml	

ERP/ERCP	240 mg I/ml	20 - 50 ml	
Herniography	240 mg I/ml	50 ml	The dosage varies with the size of the hernia
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 **Oral use** *Adults:* *Children:* - oesophagus *Prematures:* **Rectal use** - *children:*	350 mg I/ml 300 mg I/ml or 350 mg I/ml 350 mg I/ml dilute with tapwater to 100-150 mgI/ml	Individual 2-4 ml/kg b.w. 2-4 ml/kg b.w. 2-4 ml/kg b.w. 5-10 ml/kg b.w.	 Max. dose 50 ml Max. dose 50 ml Example: Dilute Omnipaque 240, 300 or 350 with tap-water 1:1 or 1:2
CT- enhancement **Oral use** - *adults:* - *children:* **Rectal use** - *children*:	 Dilute with tap water to ~6mgI/ml Dilute with tap water to ~6mgI/ml Dilute with tap water to ~6mgI/ml	 800-2000 ml of the diluted solution over a period of time 15-20 ml/kg b.w. of the diluted solution individual	 Example: Dilute Omnipaque 300 or 350 with tap water 1:50

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.

Premedication with corticosteroids or histamine H_1 and H_2 antagonists might be considered in patients at risk for intolerance, they may, however, not prevent anaphylactic shock, they may actually mask initial symptoms. 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 β-blockers may present with atypical symptoms of anaphylaxis which may be interpreted as vagal reaction.

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.

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).

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.

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, in patients with cerebral oedema, acute demyelinisation or advanced cerebral atherosclerosis.

Neurological symptoms caused by metastases, degenerative or inflammatory processes can be aggravated by application of contrast media. Intra-arterial injection of contrast media may induce vasospasm with resulting cerebral ischaemic phenomena.

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.

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:

Normal serum creatinine (<130µmol/litre)/normal renal function: Administration of metformin should be stopped at the time of administration of contrast medium and should not be resumed for 48 hours and only be restarted if 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 48 hours later 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. 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 lactacidosis.

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.

Hepatic reactions:

A potential risk of transient hepatic dysfunction exists. 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.

Following injection of an iodinated contrast agent, there is also a risk of induction of hypothyroidism.

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.

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:

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. It is advisable to monitor thyroid function. 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.

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.

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

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.

The listed frequencies are based on internal clinical documentation and published large scale studies, comprising more than 90,000 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)

Immune system disorders:
Rare: Hypersensitivity (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.

Not known: Anaphylactic /anaphylactoid reaction, anaphylactic/anaphylactoid shock

Nervous system disorders:
Rare: Headache
Very rare: Dysgeusia (transient metallic taste)
Not known: Syncope vasovagal

Cardiac disorders:
Rare: Bradycardia

Vascular disorders:
Very rare: Hypertension, hypotension

Gastrointestinal disorders:
Uncommon: Nausea
Rare: Vomiting
Very rare: Diarrhoea, abdominal pain/discomfort
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

Nervous system disorders:
Rare: Dizziness, paresis, paralysis, photophobia, somnolence
Very rare: Seizures, disturbance in consciousness cerebrovascular accident, sensory abnormalities (including hypoaesthesia), paraesthesia, tremor.
Not known: Transient motor dysfunction (including speech disorder, aphasia, dysarthria), transient contrast induced encephalopathy (including transient memory loss, coma, stupor, retrograde amnesia), disorientation, brain oedema**.**

Eye disorders:
Rare: Visual impairment
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
Not known: Severe cardiac complications (including cardiac arrest**,** cardio-respiratory arrest), cardiac failure, spasm of coronary arteries, cyanosis, chest pain

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, acute pancreatitis

Skin and subcutaneous tissue disorders:
Rare: Rash, pruritus, urticaria
Not known: 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

Renal and urinary system disorders:
Rare: Impairment of renal function including acute renal failure

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

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 minimize pressure loss.

Psychiatric disorders:
Not known: Confusion, agitation

Nervous system disorders:
Very common: Headache (may be severe and prolonged)
Uncommon: Aseptic meningitis (including chemical meningitis).
Rare: Seizures, dizziness
Not known: Electroencephalogram abnormal, meningism, status epilepticus, transient contrast-induced encephalopathy (including transient memory loss, coma, stupor, retrograde amnesia), 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

(c) 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 that may cause neurological reactions. They may include convulsions, transient motor or sensory disturbances, transient confusion, transient memory loss, and encephalopathy (see section 4.4).

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).

(d) 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.
Any suspected adverse events should be reported to the Ministry of Health according

to the National Regulation by using an online form https://sideeffects.health.gov.il/

And emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

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 ($t_{1/2}$ ~ 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

The expiry date of the product is indicated on the packaging materials

6.4. Special Precautions for Storage

OMNIPAQUE should be stored up to 30ºC protected from light. Vials are intended for single use any unused portions must be discarded.

6.5 Nature and content of container

Glass vials and bottles:
The product is filled in injection vials (20 ml) and infusion bottles (50, 100, 200 ml). Both containers are made of colourless highly resistant borosilicate glass (Ph. Eur. Type I), closed with chlorobutyl rubber or bromobutyl 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. The bottles of 50, 100, 200 and 500 ml are closed with chlorobutyl or bromobutyl stoppers (Ph.Eur.Type I), and supplied with a plastic screw cap, which is provided with a tamper proof ring.

Presentations:

Glass vials/bottles:
240 mg I/ml: 6 vials of 20 ml
25 vials of 20 ml
10 bottles of 50 ml
10 bottles of 100 ml
6 bottles of 200 ml

300 mg I/ml: 6 vials of 20 ml
25 vials of 20 ml
10 bottles of 50 ml
10 bottles of 100 ml
6 bottles of 200 ml

350 mg I/ml: 6 vials of 20 ml
25 vials of 20 ml
10 bottles of 50 ml

10 bottles of 100 ml
6 bottles of 200 ml

Polypropylene bottles:
300 mg I/ml: 10 x 50 ml
10 x 100 ml
10 x 200 ml
6 x 500 ml

350 mg I/ml: 10 x 50 ml
10 x 100 ml
10 x 200 ml
6 x 500 ml

6.6 Special precautions for disposal and other handling

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. Vials are intended for single use only; any unused portions must be discarded.

Polypropylene bottles of 500 ml

- The 500 ml contrast medium bottles should only be used in connection with auto injectors/pumps approved for this volume.
- A single piercing procedure should be used.
- Remove the plastic screw cap by tearing off the pull ring.
- After cleaning the stopper with a pad soaked in sporicidal solution followed by 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 at the end of the day.
- Instructions from the manufacturer of the auto injector/pump must be followed.

7. MARKETING AUTHORISATION HOLDER

Eldan Electronic Instrument Co. Ltd.
Hashiloach 6
P.O.B 7641
Petach Tiqva 49170
Israel

8. MANUFACTURER

GE Healthcare AS
P.O.B 4220 Nydalen
NO-0401 Oslo
NORWAY

9. MARKETING AUTHORISATION NUMBER

Omnipaque 240: 017 09 23120
Omnipaque 300: 017 10 23121
Omnipaque 350: 017 11 23122

Revised in March, 2021 according to MOH's guidelines.