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GE Healthcare

OMNIPAQUE™

IOHEXOL

1 NAME OF THE MEDICINAL PRODUCT

OMNIPAQUE injection 140 mg I/ml, 180 mg I/ml, 200 mg I/ml, 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)	140 mg I/ml	302 mg equiv. 140 mg I
Iohexol (INN)	180 mg I/ml	388 mg equiv. 180 mg I
Iohexol (INN)	200 mg I/ml	431 mg equiv. 200 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

Iohexol is a non-ionic, monomeric, tri-iodinated, 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 ** Osm/kg H_2O 37°C	Viscosity (mPa·s)	
		20°C	37°C
140 mg I/ml	0.29	2.3	1.5
180 mg I/ml	0.36	3.2	2.0
200 mg I/ml	0.41	3.8	2.4
240 mg I/ml	0.51	5.6	3.3
300 mg I/ml	0.64	11.6	6.1
350 mg I/ml	0.78	23.3	10.6

** Method: Vapour - pressure osmometry.

This medicinal product contains 0.012 mg sodium per ml, i.e. essentially sodium free.

For a full list of Excipients, see Section **6.1 LIST OF EXCIPIENTS**.

3 PHARMACEUTICAL FORM

Solution for injection.
Omnipaque injection is supplied ready to use as clear, colourless to pale yellow, sterile aqueous solutions.

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 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 varies depending on the type of examination, age, weight, cardiac output and general condition of the patient and the technique used. Usually the same iodine concentration and volume is used as with 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/Investigation	Concentration	Volume	Comments
Intravenous use			
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 3 ml/kg	
Children > 7 kg	240 mg I/ml or 300 mg I/ml	3 ml/kg 2 ml/kg	max 40 ml
Phlebography (leg)	240 mg I/ml or 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	140 mg I/ml or 200 mg I/ml or 240 mg I/ml or 300 mg I/ml or 350 mg I/ml	100 - 400 ml 100 - 300 ml 100 - 250 ml 100 - 200 ml 100 - 150 ml	Total amount of iodine usually 30 - 60 g
Children	240 mgI/ml or 300 mgI/ml	2-3 ml/kg bw up to 40ml 1-3 ml/kg bw up to 40ml	In a few cases up to 100 ml may be given.

Guidelines for intra-arterial use

Indication/Investigation	Concentration	Volume	Comments
Intra-arterial use			
Arteriographies			
Arch aortography	300 mg I/ml	30 - 40 ml/inj	Volume pr. injection depends on the site of injection
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			
Adults			
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	
Children	300 mg I/ml or 350 mg I/ml	depending on age, weight and pathology	max 8 ml/kg
Digital subtraction angiography	140 mg I/ml or 200 mg I/ml or 240 mg I/ml or 300 mg I/ml	1 - 15 ml/inj 1 - 15 ml/inj 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/Investigation	Concentration	Volume	Comments
Intrathecal use			
Myelography			
Lumbar and thoracic myelography (lumbar injection)	180 mg I/ml or 200 mg I/ml or 240 mg I/ml	10 - 15 ml 10 – 15 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)	180 mg I/ml or 200 mg I/ml or 240 mg I/ml	5 - 15 ml 5 – 15 ml 4 - 12 ml	
Paediatric myelography			
<2 years	180 mg I/ml	2 - 6 ml	
2-6 years	180 mg I/ml	4 - 8 ml	
>6 years	180 mg I/ml	6 - 12 ml	

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

Guidelines for Body cavities

Indication/Investigation	Concentration	Volume	Comments
Use in body cavities			
Arthrography	200 mg I/ml or 240 mg I/ml or 300 mg I/ml or 350 mg I/ml	5 – 20 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	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	180 mg I/ml or 200 mg I/ml or 350 mg I/ml	individual individual individual	
Children			
- Oesophagus	300 mg I/ml or 350 mg I/ml	2-4 ml/kg bw 2-4 ml/kg bw	Max. dose 50 ml Max. dose 50 ml
- Ventricle/follow through	140 mg I/ml	4-5 ml/kg bw	
Prematures	350 mg I/ml	2-4 ml/kg bw	
Rectal use			
Children	140 mg I/ml or dilute with tap-water to 100-150 mg I/ml	5-10 ml/kg bw	Example: Dilute Omnipaque 240, 300 or 350 with tap-water 1:1 or 1:2
CT- enhancement			
Oral use			
Adults	Dilute with tap-water to ~6 mg I/ml	800 -2000 ml of the diluted solution over a period of time	Example: Dilute Omnipaque 300 or 350 with tap-water 1:50
Children	Dilute with tap-water to ~6 mg I/ml	15-20 ml/kg bw of the diluted solution	

Rectal use Children	Dilute with tap-water to ~6 mg I/ml	individual	

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (See Section **6.1 LIST OF 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 angioedema, 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. These patients may also present with atypical symptoms of anaphylaxis which may be misinterpreted 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 angioedema, 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.

Coagulopathy
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.

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.

The examination shall be kept as short as possible.

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

In vitro, non-ionic contrast media have a weaker coagulation inhibiting effect than ionic contrast media.

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 and elderly patients and patients in bad general condition. Young infants (age <1 year) and especially neonates are susceptible to electrolyte disturbance and haemodynamic alterations.

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 kidney injury.

Cardio-circulatory reactions

Care should also be taken in patients with serious cardiac disease or 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

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

Encephalopathy has been reported with the use of contrast media, such as iohexol. Contrast encephalopathy may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema. 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 cerebral 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.

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. 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 increase in serum creatinine and acute kidney injury. 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, paraproteinaemias (myelomatosis and Waldenström’s macroglobulinaemia 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, particular in those with impaired renal function.
To reduce the risk of lactic acidosis, serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium and the following precautions undertaken in the following circumstances:

(1) Patients with eGFR equal or greater than 60 mL/min/1.73m2 (CKD 1 and 2) can continue to take metformin normally.

(2) Patients with eGFR 30-59 mL/min/1.73m2 (CKD 3)
   - Patients receiving intravenous contrast medium with eGFR equal or greater than 45 mL/min /1.73m2) can continue to take metformin normally
   - In patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73m2 metformin should be discontinued 48 hours before contrast medium and should only be restarted 48 hours after contrast medium if renal function has not deteriorated.

(3) In patients with eGFR less than 30 mL/min/1.73m2 (CKD 4 and 5) or with an intercurrent illness causing reduced liver function or hypoxia metformin is contraindicated iodinated contrast media should be avoided.

(4) In emergency patients in whom renal function is either impaired or unknown, the physician shall weigh out risk and benefit of an examination with a contrast medium. Metformin should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

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 medium for radiological procedures.

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

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

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.

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

Intrathecal use:
Following myelography the patient should rest with the head and thorax elevated by 20° for one hour. Thereafter he/she may ambulate carefully but bending down must be avoided. The head and thorax should be kept elevated for the first 6 hours if remaining in bed. Patients suspected of having a low seizure threshold should be observed during this period. Outpatients should not be completely alone for the first 24 hours.

Paediatric population:
Special attention should be paid to paediatric patients below 3 years of age because an incident underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. The incidence of hypothyroidism in patients younger than 3 years of age exposed to iodinated contrast media has been reported between 1.3% and 15% depending on the age of the subjects and the dose of the iodinated contrast agent and is more commonly observed in neonates and premature infants. Neonates may also be exposed through the mother during pregnancy. Thyroid function should be evaluated in all paediatric patients younger than 3 years of age following exposure to iodinated contrast media. If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalized.

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.

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.

4.5 INTERACTIONS WITH OTHER MEDICAMENTS 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 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**)

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 medium, should be carefully weighed against the possible risk. Omnipaque should not be used in pregnancy unless the benefit outweighs 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.

In neonates who have been exposed to iodinated contrast media in utero, it is recommended to monitor thyroid function (see Section **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Breast-feeding:
Contrast media are poorly excreted in human breast milk and minimal amounts are absorbed by the intestine. Harm to the nursing infant is therefore unlikely. 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 and use machines for one hour after the last injection or during the first 24 hours following intrathecal examination. However, individual judgement

must be performed if there are persistent post-myelographic 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 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)

Immune system disorders
Rare: Hypersensitivity (may be life-threatening or fatal), including dyspnoea, rash, erythema, urticaria, pruritus, skin reaction, conjunctivitis, coughing, rhinitis, sneezing, vasculitis, angioedema, laryngeal oedema, laryngospasm, bronchospasm or non-cardiogenic pulmonary oedema. They may appear either immediately after the injection 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)

Injury, poisoning and procedural complications
Not known: Iodism

Intravascular use (intra-arterial and intravenous use)
Please first read the section labelled "General". Below, only undesirable events with frequency during intravascular use of non-ionic monomeric contrast media are described.

The nature of the undesirable effects specifically seen during intra-arterial 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, stupor, sensory abnormalities (including hypoaesthesia), paraesthesia, tremor
Not known: Transient motor dysfunction (including speech disorder, aphasia, and dysarthria), transient contrast induced encephalopathy (including transient memory loss, disorientation, coma, retrograde amnesia, hemiparesis and brain oedema)

Eye disorders
Rare: Visual impairment (including diplopia, blurred vision)
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

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

Gastrointestinal disorders
Rare: Diarrhoea
Not known: Aggravation of pancreatitis

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

Renal and urinary 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 non-ionic 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

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, hemiparesis), 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).

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.

Anaphylactoid reaction and anaphylactoid shock may lead to profound hypotension and related symptoms and signs like hypoxic encephalopathy, renal and hepatic failure.

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.

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 breastfed 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.

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 high-concentration contrast media 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

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. The

elimination half-life is approximately 2 hours in patients with normal renal function. No metabolites have been detected.
The protein binding of Omnipaque is so low (less than 2%) that it has no clinical relevance and can therefore be neglected.

5.3 PRECLINICAL 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. The cardiovascular and neurotoxicity are low. The histamine release ability and the anticoagulant activity have been shown to be less than for ionic contrast media.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The following excipients are included:

Trometamol, sodium calcium edetate, hydrochloric acid (pH adjustment) and water for injections.

The pH of the product is 6.8 - 7.6.

6.2 INCOMPATIBILITIES

Although no incompatibility has been found, Omnipaque should not be directly mixed with other drugs. A separate syringe should be used.

6.3 SHELF LIFE

See expiry date printed on the label.

6.4 STORAGE CONDITIONS

Omnipaque should be stored according to instructions on the label. The product in glass vials and bottles may be stored at 37 °C for up to 1 month prior to use.

The product in 40, 50, 75, 100, 150, 175, 200 and 500 ml poly- propylene bottles may be stored at 37 °C for up to 1 month prior to use.

10, 15 and 20 ml polypropylene bottles may be stored at 37 °C for up to 1 week prior to use.

6.5 NATURE AND CONTENT OF CONTAINER

Glass vials and bottles:

The product is filled in injection vials (10, 15, 20 ml) and infusion bottles (40, 50, 75, 100, 200 and 500 ml). Both containers are made of colourless highly resistant borosilicate glass (Ph. Eur. Type I), closed with halobutyl (chlorobutyl or bromobutyl) 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. The bottles of 10, 15, 20, 40 and 50 ml are rigid stand-up bottles with a twist-off top.
The bottles of 50, 75, 100, 150, 175, 200 and 500 ml are closed with halobutyl (chlorobutyl or bromobutyl) rubber stoppers (Ph. Eur. Type I), and supplied with a plastic screw cap, which is provided with a tamper proof ring.

PRESENTATIONS

Glass vials/bottles

140 mg I/ml	10 bottles of 50 ml
	6 bottles of 200 ml

180 mg I/ml	10 vials of 10 ml
	10 vials of 15 ml
	10 bottles of 50 ml

240 mg I/ml	10 vials of 10 ml 6 vials of 20 ml 25 vials of 20 ml 10 bottles of 50 ml 6 bottles of 200 ml 6 bottles of 500 ml

300 mg I/ml	10 vials of 10 ml 6 vials of 20 ml 25 vials of 20 ml 10 bottles of 50 ml 10 bottles of 100 ml 6 bottles of 150 ml 6 bottles of 500 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 150 ml 6 bottles of 200 ml 6 bottles of 500 ml

Polypropylene bottles

140 mg I/ml	10 bottles of 50 ml

	10 bottles of 100 ml 10 bottles of 200 ml

180 mg I/ml	10 bottles of 10 ml 10 bottles of 15 ml 10 bottles of 50 ml

200 mg I/ml	10 bottles of 100 ml

240 mg I/ml	10 bottles of 10 ml 10 bottles of 20 ml 10 bottles of 50 ml 10 bottles of 100 ml 10 bottles of 200 ml 6 bottles of 500 ml

300 mg I/ml	10 bottles of 10 ml 10 bottles of 20 ml 10 bottles of 40 ml 10 bottles of 50 ml 10 bottles of 75 ml 10 bottles of 100 ml 10 bottles of 150 ml 10 bottles of 175 ml 10 bottles of 200 ml 6 bottles of 500 ml

350 mg I/ml	10 bottles of 20 ml 10 bottles of 40 ml 10 bottles of 50 ml 10 bottles of 75 ml 10 bottles of 100 ml 10 bottles of 150 ml 10 bottles of 175 ml 10 bottles of 200 ml 6 bottles of 500 ml

Please note:
In certain countries some of the indications may not be approved by the health authorities, and some of the concentrations and package sizes may not be available.

6.6 INSTRUCTIONS FOR USE/HANDLING

Like all parenteral products, Omnipaque should be inspected visually for particulate contamination, 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.

Omnipaque may be warmed to body temperature (37°C) before administration.

Additional instruction for autoinjector/pump:
The 500 ml contrast medium bottles should only be used in connection with auto injectors/pumps approved for this volume.
A single piercing procedure should be used.
The line running from this auto injector/pump to the patient must be exchanged after each patient. Any unused portions of the contrast medium remaining in the bottle and all connecting tubes must be discarded at the end of the day. When convenient, smaller bottles can also be used. Instructions from the manufacturer of the auto injector/pump must be followed.

7 MANUFACTURED BY

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9 DATE OF (PARTIAL) REVISION OF THE TEXT

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