# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

<Product name> 350 mg Iodine/ml solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml solution contains 755 mg Iohexol (equivalent to 0.919 mmol Iohexol), equivalent to 350 mg Iodine.

1 bottle with 50ml contains 37.8g Iohexol(equivalent to 46.0mmol Iohexol),equivalent to 17.5g Iodine.
1 bottlewith 75 ml contains 56.63 g Iohexol (equivalent to 69.0 mmol Iohexol),equivalent to 26.25 g Iodine.
1 bottle with 100 ml contains 75.5 g Iohexol (equivalent to 91.9 mmol Iohexol), equivalent to 35.0 g Iodine.
1 bottle with 200 ml contains 151.0 g Iohexol (equivalent to 183.8 mmol Iohexol), equivalent to 70.0 gIodine.
1 bottle with 500 ml contains 377.5 g Iohexol (equivalent to 459.7 mmol Iohexol), equivalent to 175.0 gIodine.

Excipient(s) with known effect: 0.1 mg/ml sodium calcium edetate.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection

Iohexol is a non-ionic, monomeric, triiodinated, water –soluble X-ray contrast medium. <Product name> 350 mg Iodine/ml is a clear, colourless to pale yellow sterile solution free from visible particles.

The physico-chemical properties of <Product name> 350 mg Iodine/ml are as follows:

| | |
|---|---|
| pH: | 6.8 – 7.7 |
| Osmolality (Vapour-pressure osmometry): | 0.747-0.913 Osm/kg |
| Viscosity at 37°C: | 8.5 – 10.5 mPa·s |
| Viscosity at 20°C: | 21 mPa·s |

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

<Product name> 350 mg Iodine/ml is a radiographic contrast medium indicated for visualisation of abnormal structures or lesions and differentiation between healthy and pathological tissue in adults, neonates, infants, children and adolescents for

- urography,
- CT- enhancement,
- arteriography, phlebography, cardioangiography,
- cervical myelography and computed tomography of the basal cisterns after subarachnoid instillation,
- application in body cavities: arthrography, hysterosalpingography, sialography, and examination of gastrointestinal tract.

## 4.2 Posology and method of administration

Posology

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. A total dose of 1.5 g iodine per kg body weight should not be exceeded per examination day. Adequate hydration should be assured before and after administration as for other contrast media.

The following dosages may serve as a guide.

The dosage for children, if not indicated otherwise, depends on their age and weight and is defined by the attending physician.

**Guidelines for intravenous use**

| **Indication** | **Concentration** | **Volume** | **Comments** |
|---|---|---|---|
| Urography<br>Adults<br><br>Children < 7 kg<br>Children and adolescents >7 kg | <br>300 mg I/ml<br>or 350 mg I/ml<br>300 mg I/ml<br>300 mg I /ml | <br>40 - 80 ml<br>40 - 80 ml<br>3 ml/ kg<br>2 ml/kg<br>(max 40 ml) | <br>80 ml may be exceeded in selected cases |
| Phlebography (leg) | 300 mg I /ml | 20 – 100 ml/leg | |
| Digital subtraction angiography | 300 mg I/ ml<br>or 350 mg I/ml | 20 - 60 ml/ inj.<br>20 - 60 ml/ inj. | |
| CT-enhancement<br>Adults<br><br>Children and adolescents | <br>300 mg I/ml<br>or 350 mg I/ml<br>300 mg I/ml | <br>100 - 200 ml<br>100 – 150 ml<br>1 - 3 ml/kg b.w. up to 40 ml | <br>Total amount of iodine usually 30-60 g<br>In a few cases up to 100 ml may be given |

**Guidelines for intra-arterial use**

| **Indication** | **Concentration** | **Volume** | **Comments** |
|---|---|---|---|
| Arteriographies<br>Arch aortography<br><br><br><br>selective cerebral<br>Aortography<br>femoral<br><br>various | <br>300 mg I/ml<br><br><br><br>300 mg I /ml<br>350 mg I/ ml<br>300 mg I/ ml<br>or 350 mg I/ml<br>300 mg I/ml | <br>30 - 40 ml /inj.<br><br><br><br>5 - 10 ml /inj.<br>40 - 60 ml/inj.<br>30 - 50 ml/inj.<br><br>depending on type of examination | <br>Volume per injection depends on the site of injection |
| Cardioangiography<br>Adults<br>Left ventricle and aortic root inj. | <br><br>350 mg I/ ml | <br><br>30 – 60 ml/inj. | |

| | | | |
|---|---|---|---|
| Selective coronary arteriography<br>Children and adolescents | 350 mg I/ml<br>300 mg I/ml<br>or 350 mg I/ml | 4 – 8 ml/ inj.<br>depending on age, weight and pathology (max 8 ml/kg) | |
| Digital subtraction angiography | 300 mg I/ ml | 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 |
|---|---|---|---|
| Cervical meyelography (lumbar injection) | 300 mg I/ml | 7 - 10 ml/inj. | |
| Cervical myelography (lateral cervical injection) | 300 mg I /ml | 6 - 8 ml | |

To minimise 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<br>or 350 mg I/ml | 5 - 15 ml<br>5-10 ml | |
| Hysterosalpingography | 300 mg I/ml | 15 - 25 ml | |
| Sialographie | 300 mg I/ml | 0.5 – 2 ml | |
| Gastrointestinal studies<br>**Oral use**<br>*Adults*<br>*Children and adolescents*<br>Oesophagus<br><br>*Prematures*<br>**Rectal use**<br>*Children and adolescents* | <br><br>350 mg I/ml<br><br>300 mg I/ml<br>or 350 mg I/ ml<br>350 mg I/ml<br><br>dilute with tap water to 100 – 150 mg I/ml | <br><br>individual<br><br>2 - 4 ml/ kg b.w.<br>2 - 4 ml/ kg b.w.<br>2 – 4 ml/kg b.w.<br><br>5 – 10 ml/ kg b.w. | <br><br><br><br>Max. Dose 50 ml<br>Max. Dose 50 ml<br><br><br>Example: Dilute <Product name> 300 mg/ml or 350 mg/ml with tap water 1:1 or 1:2 |
| CT-enhancement<br>**Oral use**<br>*Adults*<br><br><br>*Children and adolescents* | <br><br>Dilute with tap water to about 6 mg I/ ml<br><br>Dilute with tap water to about 6 mg I/ ml | <br><br>800 – 2000 ml of the diluted solution over a period of time<br><br>15 – 20 ml/ kg b.w. of the diluted solution | <br><br>Example: Dilute <Product name> 300 mg/ml or 350 mg/ml with tap water 1:50 |

| | | | |
|---|---|---|---|
| **Rectal use**<br>*Children and adolescents* | Dilute with tap water to about 6 mg I/ ml | individual | |

Special populations

*Renal impairment/ hepatic impairment*

Particular caution is required in patients with concomitant hepatic insufficiency and renal insufficiency, which increases the risk of retention of the contrast agent.

*Elderly (aged 65 years and above)*
No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Method of administration
For intravenous, intra-arterial and intrathecal use, use in body cavities and oral use.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Manifest thyrotoxicosis.
- Serious reactions in previous use of Iohexol.
- <Product name> 300 mg Iodine/ml and <Product name> 350 mg Iodine/ml solutions are not recommended for myelography of children up to 14 years.

## 4.4 Special warnings and precautions for use

Special precautions for use of non-ionic contrast media in general
The patient should not eat two hours before examination.

General Warnings
Iodinated contrast media should only be used after precise clinical indication considering possible risk factors of the examined patient. Strict indication and special care is required in patients with

- known allergic disposition
- latent hyperthyreosis, euthyroid goiter
- renal impairment in particular in combination with severe liver dysfunction.
- severe cardiovascular disease
- bronchial asthma
- diabetes mellitus
- cerebral convulsive disorder
- advanced cerebral atherosclerosis
- acute cerebral infarction
- acute intracranial bleeding or conditions accompanied by impairment of the blood-brain barrier and cerebral oedema
- bad general condition, dehydration
- dys- or paraproteinaemia
- phaeochromocytoma

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 H1 and H2 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 Iohexol 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 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 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.

*Before the investigation*
- ask the patient about previous reactions to contrast media or allergies,
- consider premedication with antihistamines and/or glucocorticoids in patients with the highest risk / known intolerance. However, they cannot prevent the occurrence of serious or fatal anaphylactic shock.

*During the investigation*
- provide medical monitoring
- maintain a venous access for emergency treatment in the event of a reaction.

*After the examination*
- the patient should be kept under supervision for at least 30 minutes, during which the majority of serious adverse effects occur. All physicians and nursing staff must be informed of adverse reactions as well as general and medicinal emergency measures. Appropriate facilities should be available for coping with any complication of the procedure, as well as resuscitative equipment and emergency medication for emergency treatment of severe reaction to the contrast medium itself.
- The patient should be informed that allergic reactions may develop up to several days after the procedure; in such case, a physician should be consulted immediately.

<u>Coagulopathy</u>
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.
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 minimise 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).

<u>Hydration</u>
In patients with cardiac insufficiency intravasal injection of contrast media can induce pulmonary oedema. 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. 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.

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 preexisting 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, 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)/renal impairment*: 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. A pH < 7.25 or a lactic acid level of >5 mmol/litre are indicative for lactic acidosis. The patient should be observed for symptoms of lactic acidosis. These include vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhea 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 thyreotoxic 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, which are present 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. However, delayed reactions may occur.

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 in such patients. Thyroid function should be checked in neonates during the first week of life, following administration of iodinated contrast agents to the mother during pregnancy. Repeat testing of thyroid function is recommended at 2 to 6 weeks of age, particularly in low birth weight newborn or premature newborn. See also section 4.6.

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.

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

## 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 phenothiazine derivates, including neuroleptics, tricyclic antidepressants, histamine H1-antagonists, MAO-inhibitors and analeptics 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 Iohexol 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. <Product name> 350 mg Iodine/ml 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.
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.

Fertility
Clinical data on fertility are not available (see section 5.3).

## 4.7 Effects on ability to drive and use machines

No studies on the ability to drive or use machines have been performed. There is no known effect on the ability to drive or operate machines. However, 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 judgment 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.

lodism 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:**

| | |
|---|---|
| Common: | Conjunctivitis, sneezing |
| Rare: | Hypersensitivity (including dyspnoea, rash, erythema, urticaria, pruritus, skin reaction, coughing, rhinitis, vasculitis, angioneurotic oedema, 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. |
| 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: Hyperthyroidism, 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, and tremor.
Not known: Transient motor dysfunction (including speech disorder, aphasia, and dysarthria), transient contrast induced encephalopathy (including transient memory loss, 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, 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, erythema multiforme, 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, acute pancreatitis

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

**Renal and urinary 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, 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 minimise 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, motor dysfunction (including speech disorder, aphasia, dysarthria), paraesthesia, hypoesthesia, sensory disturbance, transient contrast induced encephalopathy (including transient memory loss, coma, stupor, retrograde amnesia).

**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 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).

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. Transient hypothyroidism in a premature breast fed infant has been reported. The nursing mother was repeatedly exposed to Iohexol (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 the national reporting system listed in Appendix V*.

## 4.9 Overdose

Preclinical data indicate a high safety margin for Iohexol and no fixed uper dose level has been established for routine intravascular use. Symtomatic overdosing is unlikely in patients with normal renal function, unless the patient has received more than 2000 mg Iodine/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 ($t_{½} \approx 2$ hours). Accidental overdosing is most likely following complex angiographic procedures in children, particulary 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.

Intrathecal use:
In case of overdose it may lead to cerebral and spinal symptoms (eg seizures, myoclonus). The treatment consists in protection of all vital functions and symptomatic therapy.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: X-Ray Contrast Media, iodinated; Watersoluble, nephrotropic, low osmolar X-ray contrast media, ATC code: V08A B02

<Product name> is a triiodinated, non-ionic, water-soluble contrast medium with a molecular weight of 821.1 g/mol. The contrast effect is achieved by the stable bound iodine, which absorbs X-rays.
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

- Distribution

After intravascular administration Iohexol is rapidly distributed in the extracellular space. The half-life is 9 ± 9 minutes.

The plasma protein binding is 1.5 ± 0.3% for a concentration of 1.2 mg Iodine/ml plasma. It has no clinical relevance and can therefore be neglected. Animal studies have shown that Iohexol can not break through intact blood-brain barrier, but to a very small extend the placental barrier.

- Biotransformation

No metabolites have been observed in humans after application of relevant clinical doses.

- Elimination

Iohexol is eliminated primarily by glomerular filtration. In a study with 20 male subjects (age 18-49 years) with normal renal function, the mean elimination half-life was 121 minutes (108 – 126) regardless of the administered dose.

Close to 100 per cent of the intravenously injected iohexol is excreted unchanged through kidneys within 24 hours. The maximum urinary concentration of iohexol appears within approximately 1 hour after injection.

In a study with 10 subjects (age 70 ± 16 years) with age-related reduced renal function (total clearance 86±29 ml/min) 87% were eliminated within 24 hours and 91% within 6 days of the injected dose of 300 mg Iodine/ kg body weight.

- Particularities

In end-stage renal disease contrast media can be eliminated by dialysis.

- Administration as part of ERCP

Significant amounts of contrast agent can be absorbed as part of ERCP. Quantitative data of Iohexol are not available. For possible side effects see section 4.4 and section 4.8.

- Intrathecal use

Iohexol is rapidly excreted from the lumbar subarachnoid space in the epidural veins. Maximum serum concentrations are observed in patients 2.2 (1.7 to 2.2) hours after application.

### 5.3 Preclinical safety data

Iohexol has a very low acute intravenous toxicity in mice and rats.
Animal studies investigating systemic tolerance with single and repeated daily intravenous administration did not yield findings, which would argue against in general single diagnostic use in humans**.**

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. Furthermore, there was no mutagenic effect detected.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Trometamol
Sodium calcium edetate
Hydrochloric acid (pH adjustment)
Water for Injection

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## 6.3 Shelf life

5 years

After first opening: Any unused portion must be discarded. Use the bottles for one patient only. For single withdrawal only.

From a microbial point of view, the product should be used immediately, unless the opening procedure eliminates the risk of microbial contamination. If not used immediately, in-use storage times and conditions prior to use are in the responsibility of the user and should normally not be longer than 12 hours at 20°C or 37°C condition.

## 6.4 Special precautions for storage

Keep the bottle in outer carton in order to protect from light. Protect from secondary X-rays. The product may be stored unopened in the original container at 37°C for up to 3 months. After this period the solution has to be discarded, even though the shelf-life of the products mentioned on the container and carton box has not been reached. The date of beginning of tempering has to be reported in the designated filed on the bottle. The product must not be used after shelf-life.
For storage conditions after first opening of the medicinal product, see section 6.3

## 6.5 Nature and contents of container

The product is filled in 100, 250 and 500 ml infusion bottles. The containers are made of colourless glass bottles (Ph.Eur. II), closed with red chlorobutyl rubber stopper (Ph.Eur. Type I), and sealed with aluminium caps with garnet polypropylene disk.

10 bottles with 75 ml filling volume
10 bottles with 100 ml filling volume
10 bottles with 200 ml filling volume
5 bottles with 500 ml filling volume

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Like all parenteral products, <Product name> 350 mg Iodine/ml should be inspected visually for particulate matter, discolouration and the integrity of the container prior to use.
Any bottle is for single withdrawal only. The product should be drawn into the syringe respectively the bottle connected to the automatic application system immediately before use. The rubber should never be pierced more than once. If the medicine is intended to be used with an automatic application system, its suitability for the intended use has to be demonstrated by the manufacturer of the medicinal device. Any unused portions must be discarded. <Product name> 350 mg Iodine/ml may be warmed to body temperature (37°C) before administration. Contrast agents warmed to body temperature before administration are better tolerated and are easier injectable due to lower viscosity.

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

# 7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and address}

<{tel}>
<{fax}>
<{e-mail}>

## 8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

<[To be completed nationally]>

## 10. DATE OF REVISION OF THE TEXT

<[To be completed nationally]>