

Package leaflet: Information for the user
Iohexol 240 mg I/ml solution for injection
Iohexol 300 mg I/ml solution for injection
Iohexol 350 mg I/ml solution for injection

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Iohexol is and what it is used for
2. What you need to know before you are given Iohexol
3. How you are given Iohexol
4. Possible side effects
5. How Iohexol is stored
6. Contents of the pack and other information

1. WHAT IOHEXOL IS AND WHAT IT IS USED FOR

This medicine is for diagnostic use only. It is used only to help identify an illness. Iohexol is a 'contrast medium'. It is given using an X-ray to make the picture that your doctor takes clearer.

- Once injected, it can help your doctor tell apart normal or abnormal appearance and shape of some organs in your body.
- It can be used for X-rays of your urinary system, spine or blood vessels, including blood vessels of your heart.
- Some other people are given this medicine before or during a scan of their head or body using 'computed tomography' (also called a CAT scan). This type of scan uses X-rays.
- It can also be used to look at your salivary glands, stomach and intestine, or for looking in body cavities, such as in your joints or womb and ovarian tubes.
- It can also be used in cases of mammography examinations.

Your doctor will explain which part of your body will be scanned.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN IOHEXOL

You should not be given Iohexol if:

- You are allergic to iohexol or any of the other ingredients of this medicine (listed in section 6)
- You suffer from severe thyroid problems.

Warnings and precautions

Talk to your doctor before you are given Iohexol if:

- You have ever had an allergic reaction after a medicine similar to Iohexol, called a 'contrast medium'.
- You have any thyroid problems.
- You have ever had any allergies.
- You have asthma or if you are using beta adrenergic blocking agents.
- You have diabetes.
- You have any brain disease or tumours.
- You have or have had severe heart disease (involving heart or blood vessels) including high blood pressure, blood clots, stroke and irregular heartbeats (arrhythmia).
- You have kidney problems or both liver and kidney problems.
- You have an illness called 'myasthenia gravis' (a condition causing severe muscle weakness).
- You have a 'phaeochromocytoma' (constant or attacks of high blood pressure due to a rare tumour of your adrenal gland).
- You have 'homocystinuria' (a condition with increased excretion of the amino acid cysteine in urine).
- You have any problems with your blood or bone marrow.
- You have ever been dependent on alcohol or drugs.
- You have epilepsy.
- You are having a thyroid function test in the next weeks.

During or shortly after the imaging procedure you may experience a short-term brain disorder called contrast encephalopathy. Tell your doctor straight away if you notice any of the signs and symptoms related to this condition described in Section 4.

Contrast-enhanced mammography exposes you to higher levels of ionizing radiation than traditional mammography, however, it is still within the range defined by the international guidelines for mammography. Radiation dose depends on the thickness of the breast and the type of mammography machine used.

If you are not sure if any of the above apply to you, talk to your doctor before having Iohexol. Make sure to drink plenty of fluid before and after receiving Iohexol. This applies especially to patients with multiple myeloma (white blood cells disease), diabetes, kidney problems, patients in bad general condition, children and elderly patients. Iohexol contains sodium. This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium free'.

Children and adolescents

Make sure to drink plenty of fluid before and after receiving Iohexol. This applies especially to infants and small children. Drugs that can damage the kidneys should not be taken at the same time as Iohexol. If Iohexol has been given to the mother during pregnancy, the thyroid function of the newborn should be tested during the first week after birth. It is recommended that the testing is repeated again between 2 and 6 weeks of age in premature and low birth weight newborns.

Iohexol may be removed from an infant's body more slowly than an adult.

Young infants (less than 1 year of age) and especially newly born are susceptible to changes in certain laboratory tests (in balance in salts and minerals) and circulatory changes in blood circulation (blood flow to the heart).

Other medicines and Iohexol

Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, you should tell your doctor if you are taking:

- Any medicine containing metformin (for diabetes).

- Beta-blockers (used to treat heart problems). Beta-blockers may increase your risk of experiencing breathing difficulties and may interfere with the treatment of severe allergic reactions, which is a risk of Iohexol.
- Medicines used to control your blood pressure or heart rate (including ACE inhibitors and angiotensin antagonists).
- Or have recently been treated with certain medicines to treat immune system disorders (interleukin-2 or interferons).
- Medicines used to treat mental problems, e.g. depression (neuroleptics or tricyclic antidepressants).

This is because some medicines can affect the way Iohexol works.

Pregnancy and breast-feeding

You must tell your doctor if you are pregnant or think you may be pregnant. Your doctor will only use this product if it is considered that the benefit outweighs the risk for both the mother and the baby.

If Iohexol has been given to the mother during pregnancy, the thyroid function of the newborn should be tested during the first week after birth. It is recommended that the testing is repeated again between 2 and 6 weeks of age in premature and low birth weight newborns.

Breast-feeding may be continued normally after an examination using Iohexol.

Driving and using machines

Do not drive or use tools or machines after your last injection of Iohexol for:

- 24 hours, if it has been given into your spine, or
- One hour in all other cases.

This is because you may feel dizzy or have other signs of a reaction afterwards.

3. HOW YOU ARE GIVEN IOHEXOL

Iohexol will always be given to you by a specially trained and qualified person.

- Iohexol will always be used in a hospital or clinic.
- They will tell you anything you need to know for your safe use.

Your doctor will decide the dose that is best for you.

Iohexol will be given to you as one single injection or you may be asked to swallow it.

- After you have been given Iohexol you will be asked:
- To drink plenty of fluids afterwards (to help flush the medicine from your body), and
- To stay in or around the area where you had your scan or X-ray for around 30 minutes, and
- To stay in the clinic or hospital for one hour.

If you have any side effects during this time, tell your doctor straight away (see Section 4 'Possible Side Effects'). The advice above applies to **all patients** who have had Iohexol. If you are not sure about any of the above ask your doctor.

Iohexol may be given in lots of different ways, a description of the ways it is usually given can be found below:

Injection into an artery or vein

Iohexol will most commonly be injected into an arm vein or leg vein. Sometimes it will be given through a thin plastic tube (catheter), inserted into an artery usually in your arm or groin.

Injection into your spine

Iohexol will be injected into the space around the spinal cord to see your spinal canal. If you have been given Iohexol into your spine afterwards you will be asked to follow the advice below:

- to rest with your head and body upright for one hour, or six hours if you stay in bed, and
- to walk carefully and try not to bend down for six hours, and
- not to be completely alone for the first 24 hours after having Iohexol, if you are an outpatient and have ever had fits.

The advice above applies only if you have had Iohexol injected into your spine. If you are not sure about any of the above ask your doctor.

Use in your body cavities or joints

Body cavities may be the joints, uterus and ovarian tubes. How and where Iohexol is given will vary.

Use by mouth

For examination of the gut, stomach or small bowel, Iohexol is normally given by mouth. Iohexol may be diluted with water for these examinations.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Iohexol can cause side effects, although not everybody gets them.

Allergic reactions

If you have an allergic reaction when you are in hospital or a clinic having Iohexol, tell the doctor straight away. The signs may include:

- wheeziness, difficulty in breathing or tightness or pain in your chest
- skin rash, lumps, itchy spots, blisters on skin and in mouth, red/itchy eyes, cough, running nose, sneezing or other allergic symptoms
- swelling of your face
- dizziness or feeling faint (caused by low blood pressure)
- severe skin reactions including potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis), appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). These potentially life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin. If you have developed Stevens-Johnson syndrome or toxic epidermal necrolysis with the use of Iohexol, you must not be re-started on Iohexol at any time.

The above side effects may happen several hours or days after Iohexol is given. If any of these side effects happen after you leave the hospital or clinic, go straight to the casualty department of your nearest hospital.

A short term decrease in formation of urine due to decreased kidney function is common after Iohexol is given. This may lead to damage to the kidney.

Other side effects that you may have are listed below; these depend on how or why Iohexol was given to you. Ask your doctor if you are not sure how you were given Iohexol.

SCIENTIFIC LEAFLET

1. Name of the medicinal product

Iohexol 240 mg I/ml solution for injection
 Iohexol 300 mg I/ml solution for injection
 Iohexol 350 mg I/ml solution for injection

2. Qualitative and quantitative composition

| Active ingredient | Strength | Content per ml |
|-------------------|-------------|------------------------|
| Iohexol | 240 mg I/ml | 518 mg equiv. 240 mg I |
| Iohexol | 300 mg I/ml | 647 mg equiv. 300 mg I |
| Iohexol | 350 mg I/ml | 755 mg equiv. 350 mg I |

For the full list of excipients, see section 6.1.

The osmolality and viscosity values of Iohexol are as follows:

| Concentration | Osmolality* mOsm/kg H2O | | |
|---------------|-------------------------|------|------|
| | 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.
 Clear, colourless or light-yellow liquid (solution).

4. Clinical particulars

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

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

4.2 Posology and method of administration

The dosage depends on the type of investigation and the technique used. Usually the same iodine concentration and volume is used as for other iodinated X-ray contrast media in current use.

Adequate hydration should be assured before and after administration as for other contrast media.

For intravenous, intra-arterial and intrathecal use, and use in body cavities. The following dosages may serve as a guide:

| Indication | Concentration | Volume |
|---|--|---|
| Urography Adults | 300 mg I/ml or 350 mg I/ml | 40-80 ml 40-80 ml |
| 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. |
| Phlebography (leg) | 240 mg I/ml or 300 mg I/ml | 20-100 ml/leg |
| Digital subtraction angiography Adults | 140 mg I/ml 300 mg I/ml or 350 mg I/ml | Up to 3 ml per kg body weight 20 - 60 ml/inj. 20 - 60 ml/inj. |
| Children | 140 mg I/ml | Dependent upon age, weight and pathology |
| Contrast-enhanced mammography (CEM) | 300 mg I/ml or 350 mg I/ml | Dose (per kg body weight) 1.5 ml/kg b.w. 1.3 ml/kg b.w. |
| CT enhancement Adults | 140 mg I/ml or 240 mg I/ml or 300 mg I/ml or 350 mg I/ml | 100-400 ml 100-250 ml 100-200 ml 100-150 ml |

Guidelines for intraarterial use

| Indication | Concentration | Volume |
|--|---|--|
| 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. |
| Various | 300 mg I/ml | depending on type of examination |
| 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 Adults Children | 240 mg I/ml or 140 mg I/ml or 300 mg I/ml 140 mg I/ml | 4 - 10 ml/inj. 1 - 15 ml/inj. 1 - 15 ml/inj. Dependent upon age, weight and pathology |

Guidelines for intraarterial use

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

For elderly patients, patients with hepatic and/or renal impairments, the usual/proposed doses for adults can be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. 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 allergic, anaphylactic, 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 personnel available for immediate treatment, should a serious reaction occur. In immediate 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 angiooedema, subglottic oedema, bronchial spasm and shock are rare. These reactions usually occur within one hour following application of the contrast medium. In rare cases, hypersensitivity may occur delayed (after hours or days), but these cases are rarely life threatening and mainly affect the skin.

Hydration:

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

Cardio-circulatory reactions:

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

This is especially applicable following intracranial, 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 intravascular injection of contrast media can induce pulmonary oedema.

CNS disturbances:

Patients with acute cerebral pathology, tumours or a history of epilepsy are predisposed for seizures and merit particular care. Also alcoholics and drug addicts have an increased risk for seizures and neurological reactions.

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

Factors which increase blood-brain barrier permeability will ease the transfer of contrast media to brain tissue and may lead to possible CNS reactions for instance encephalopathy. Caution is advised in intravascular application to patients with acute cerebral infarction or acute intracranial bleeding as well as in patients with diseases causing disturbance of the blood-brain barrier, and in patients with brain oedema, acute demyelination or advanced cerebral atherosclerosis.

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

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

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

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

Renal reactions:

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

Other predisposing factors are preceding renal failure following application of contrast media, a history of renal disease, age over 60 years, dehydration, advanced arteriosclerosis, decompensated cardiac insufficiency, high doses of contrast media and multiple injections, direct application of contrast media to the renal artery, exposure to further nephrotoxins, severe and chronic hypertension, hyperuricaemia, paraproteinaemias (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 artery angioplasty, or major surgery, until the contrast medium has been cleared.
- Dose reduction to a minimum.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

Patients on haemodialysis may receive contrast media for radiological procedures.

Correlation of the time of contrast media injection with the haemodialysis session is unnecessary.

Diabetic patients receiving metformin:

There is a risk of the development of lactic acidosis when iodinated contrast agents are administered to diabetic patients treated with metformin, particularly in those with impaired renal function. To reduce the risk of lactic acidosis, the serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast media and the following precautions undertaken in the following circumstances:

- (1) Patients with eGFR equal or greater than 60 ml/min/1.73m² (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) and with an intercurrent illness causing reduced liver function or hypoxia metformin is contraindicated and iodinated contrast media should be avoided.
- (4) In emergency patients in whom renal function is either impaired or unknown, the physician shall weigh out risk and benefit of an examination with a contrast medium. Metformin should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. It is particularly important that the patient is fully hydrated prior to contrast medium administration and for 24 hours afterwards. Renal function (e.g. serum creatinine), serum lactic acid and blood pH should be monitored, as well as the patient with regard to signs of lactic acidosis.

A pH < 7.25 or a lactic acid level of >5 mmol/litre are indicative of lactic acidosis. The patient should be observed for symptoms of lactic acidosis. These include vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea and thirst. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

Patients with disturbance of both hepatic and renal function:

Particular care is required in patients with severe disturbance of both renal and hepatic function as they may have significantly delayed contrast medium clearance. Patients on haemodialysis may receive contrast media for radiological procedures. Correlation of the time of contrast media injection with the haemodialysis session is unnecessary.

Myasthenia gravis:

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

General

(applies to all uses of Iohexol)

Common: may affect up to 1 to 10 people:

- feeling hot.

Uncommon: may affect up to 1 in 100 people:

- feeling sick (nausea)
- increased/abnormal sweating, cold feeling, dizziness/fainting
- headache.

Rare: may affect up to 1 in 1,000 people:

- allergic (hypersensitivity) reactions (may be fatal)
- slow heart rate
- pain around your stomach area, vomiting, fever

Very rare: may affect up to 1 in 10,000 people:

- momentary change in sense of taste
- high or low blood pressure, shivering (chills)
- diarrhoea
- allergic reaction (may be life-threatening or fatal), including severe allergic reaction leading to shock and collapse, see 'Allergic reactions' above for other signs

Not known: frequency cannot be estimated from the available data:

- swelling and tenderness (pain) of your salivary glands

After an injection into an artery or vein

Common: may affect up to 1 in 10 people:

- short-term changes in breathing rate, respiratory problems

Uncommon: may affect up to 1 in 100 people:

- pain and discomfort
- acute kidney injury

Rare: may affect up to 1 in 1,000 people:

- diarrhoea
- irregular heartbeats, including fast heart rate
- cough, stopped breathing, fever, general discomfort
- dizziness, feeling weak, muscle weakness
- intolerance to bright lights
- feeling abnormally tired
- skin rash and itching, reddening of the skin
- reduced eyesight
- photophobia (light sensitivity)

Very rare: may affect up to 1 in 10,000 people:

- seizures (fits), clouding consciousness, stroke, disturbance of senses (like touch), trembling, stupor (sleepy state)
- flushing
- difficulty breathing
- myocardial infarction
- chest pain

Not known: frequency cannot be estimated from the available data:

- severe skin reactions including severe rash, blistering and peeling of skin
- feeling confused, feeling disorientated, feeling agitated, restless or anxious
- overactive thyroid gland (an excess of thyroid hormones in the blood causing a variety of symptoms, as e.g. rapid heart beat, sweating, anxiety), short-term underactive thyroid gland (an abnormality of the thyroid function which later reverts to normal. Normally, no symptoms are seen).
- difficulty moving around for awhile
- speech disorders including aphasia (unable to speak), dysarthria (difficulties with pronouncing words)
- short-term blindness (hours to a few days), short-term hearing loss
- heart problems, including heart failure, spasms of the heart arteries and cyanosis (blue to purple colour of skin because of decreased oxygen)
- tightness in chest or troubled breathing, including swellings of the lungs, spasms in airways
- worsening of an inflammation of the pancreas (an organ behind the stomach) causing stomach pain that is worsened with eating
- pain and swelling of your vein, blood dots (thrombosis)
- joint pain, injection site reaction, back pain
- asthma attack
- psoriasis flare-up
- angioedema
- iodism (excessive amounts of iodine in the body) resulting in swelling and tenderness (pain) of your salivary glands
- memory loss (amnesia)
- short term brain disorder (contrast encephalopathy) which can cause headache, difficulties with vision, loss of vision, seizures, confusion, disorientation, drowsiness, loss of consciousness, coma, loss of coordination, loss of movement in one side of the body, problems with speech, memory loss and swelling of the brain
- thrombocytopenia (a condition where the platelet count is low causing the blood not to clot as well as it does normally)
- blood creatinine increased

After an injection into your spine

Very common: may affect more than 1 in 10 people:

- headache (may be severe and lasting)

Common: may affect up to 1 in 10 people:

- feeling sick (nausea), vomiting

Uncommon: may affect up to 1 in 100 people:

- inflammation of the membranes that surround the brain and spinal cord

Rare: may affect up to 1 in 1,000 people:

- seizures (fits), dizziness
- pain in arms or legs, neck pain, back pain

Not known: frequency cannot be estimated from the available data:

- feeling agitated
- feeling anxious
- feeling disorientated
- intolerance of bright light, neck stiffness
- difficulty moving around for a while, feeling confused
- disturbance of senses (like touch), short-term blindness (hours to a few days), short-term hearing loss
- tingling sensations, muscle contractions (spasms), injection site reaction
- short term brain disorder (contrast encephalopathy) which can cause headache, difficulties with vision, loss of vision, seizures, confusion, disorientation, drowsiness, loss of consciousness, coma, loss of coordination, loss of movement in one side of the body, problems with speech, memory loss and swelling of the brain.
- speech disorders including aphasia (unable to speak), dysarthria (difficulties with pronouncing words)

After use in body cavities (such as uterus and ovarian tubes, gall bladder and pancreas or hernia)

Very common: may affect more than 1 in 10 people:

- pain around your stomach area

Common: may affect up to 1 in 10 people:

- inflammation of the pancreas (an organ behind the stomach) causing stomach pain that is worsened with eating.
- abnormal amount of a substance produced by the pancreatic gland detected by lab investigation

Not known: frequency cannot be estimated from the available data:

- pain

After injection into your joints

Very common: may affect more than 1 in 10 people:

- pain where it was injected

Not known: frequency cannot be estimated from the available data:

- inflammation of the joint

After being given it by mouth

Very common: may affect more than 1 in 10 people:

- diarrhoea

Common: may affect up to 1 in 10 people:

- feeling sick (nausea), vomiting

Uncommon: may affect up to 1 in 100 people:

- pain around your stomach area

If any of the side effects gets serious, or if you notice any side effects not listed, please tell your doctor.

Additional side effects in children and adolescents:

Short-term underactive thyroid gland (transient hypothyroidism) has been reported in premature infants, neonates and in other children after receiving Iohexol. Premature infants are particularly sensitive to the effect of iodine. 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.

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW IOHEXOL IS STORED

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Iohexol contains

The active substance is Iohexol.

Iohexol 240 mg I/mL solution for injection contains 518 mg iohexol per mL (equivalent to 240 mg iodine per mL).

Iohexol 300 mg I/mL solution for injection contains 647 mg iohexol per mL (equivalent to 300 mg iodine per mL).

Iohexol 350 mg I/mL solution for injection contains 755 mg iohexol per mL (equivalent to 350 mg iodine per mL).

The other ingredients are sodium calcium edetate, trometamol, hydrochloric acid diluted and water for injection.

What Iohexol looks like and contents of the pack

Iohexol is a clear, colourless or light-yellow solution for injection. Iohexol 240 mg I/mL solution for injection comes in 50 mL and 100 mL glass bottles closed with rubber stoppers and aluminium seals with a plastic cap. 1 bottle per pack. Iohexol 300 mg I/mL solution for injection comes in 20 mL, 50 mL and 100 mL glass bottles closed with rubber stoppers and aluminium seals with a plastic cap. 1 or 10 bottles per pack.

Iohexol 350 mg I/mL solution for injection comes in 20 mL, 50 mL and 100 mL glass bottles closed with rubber stoppers and aluminium seals with a plastic cap. 1 or 6 bottles per pack.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Farmak Pharmaceuticals UK Ltd, First Floor, 47 Queen Street, Hull, HU1 1UU, United Kingdom

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Arteriography

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

Paediatric population:

Hypothyroidism or transient thyroid suppression may be observed after exposure to iodinated contrast media. Special attention should be paid to paediatric patients below 3 years of age because an incident underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. The incidence of hypothyroidism in patients younger than 3 years of age exposed to iodinated contrast media has been reported between 1.3% and 15% depending on the age of the subjects and the dose of the iodinated contrast agent and is more commonly observed in neonates and premature infants. Thyroid function should be evaluated in all paediatric patients younger than 3 years of age within 3 weeks following exposure to iodinated contrast media, especially in premature infants and neonates. If hypothyroidism is detected, thyroid function should be monitored as appropriate even when replacement treatment is given.

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

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

Contrast-enhanced mammography (CEM):

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

The concomitant use of certain neuroleptics or tricyclic antidepressants can reduce the seizure threshold and thus increase the risk of contrast medium-induced seizures. Treatment with β -blockers may lower the threshold for hypersensitivity reactions, as well as necessitating higher doses of β -agonists when treating hypersensitivity reactions. β -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. Iohexol should not be used in pregnancy unless the benefit outweighs the risk and it is considered essential by the physician.

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

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

Breast-feeding

Contrast media are poorly excreted in human breast milk and minimal amounts are absorbed by the intestine. Breast feeding may be continued normally when iodinated contrast media are given to the mother. The amount of iohexol in breast milk excreted in 24 hours after injection was 0.5% of the weight adjusted dose in a trial. The amount of iohexol ingested by the baby in the first 24 hours after injection corresponds to only 0.2% of the paediatric dose.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

The frequencies of undesirable effects are defined as follows:

Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

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 "iodine mumps" is a very rare complication of iodinated contrast media resulting in swelling and tenderness of the salivary glands for up to approximately 10 days after the examination.

Immune system disorders:

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

Very rare: Anaphylactic/anaphylactoid reaction (may be life-threatening or fatal)

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

Nervous system disorders:

Uncommon: Headache

Very rare: Dysgeusia (transient metallic taste), syncope/parosmias

Cardiac disorders:

Rare: Bradycardia

Vascular disorders:

Very rare: Hypertension, hypotension

Gastrointestinal disorders:

Uncommon: Nausea

Rare: Vomiting, abdominal pain

Very rare: Diarrhoea

Not known: Salivary gland enlargement

General disorders and administration site conditions:

Common: Feeling hot

Uncommon: Hyperhidrosis, cold feeling, vasovagal reactions

Rare: Pyrexia

Very rare: Shivering (chills)

Intravascular use (intraarterial and intravenous use)

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

Blood and lymphatic system disorders:

Not known: Thrombocytopenia

Endocrine disorders:

Not known: Thyrotoxicosis, transient hypothyroidism

Psychiatric disorders:

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

Nervous system disorders:

Rare: Dizziness, paresthesia, paralysis, somnolence

Very rare: Seizures, disturbance in consciousness, cerebrovascular accident, stupor, sensory abnormalities (including hypoaesthesia), paraesthesia, tremor

Not known: Amnesia, transient motor dysfunction (including speech disorder, aphasia, dysarthria), contrast encephalopathy (see "Description of selected adverse reactions" in section 4.8).

Eye disorders:

Rare: Visual impairment (including diplopia and blurred vision), photophobia

Not known: Transient cortical blindness

Ear and labyrinth disorders:

Not known: Transient hearing loss

Cardiac disorders:

Rare: Arrhythmia (including bradycardia, tachycardia).

Very rare: Myocardial infarction, chest pain

Not known: Severe cardiac complications (including cardiac arrest, cardiorespiratory 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

Very rare: Cough, respiratory arrest

Very rare: Dyspnoea

Not known: Severe respiratory symptoms and signs, pulmonary oedema, acute respiratory distress syndrome, bronchospasm, laryngospasm, apnoea, aspiration, asthma attack

Gastrointestinal disorders:

Rare: Diarrhoea

Not known: Aggravation of pancreatitis

Skin and subcutaneous tissue disorders:

Rare: Rash, pruritus, urticaria

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

Musculoskeletal and connective tissue disorders:

Not known: Arthralgia, muscular weakness, musculoskeletal spasm, back pain

Renal and urinary system disorders:

Uncommon: Acute kidney injury

Not known: Blood creatinine increased

General disorders and administration site conditions:

Uncommon: Pain and discomfort

Rare: Asthenic conditions (including malaise, fatigue).

Not known: Administration site reactions, including extravasation

Injury, poisoning and procedural complications:

Not known: Iodism

Intrathecal use

Please first read the section labelled "General". Below, only undesirable events with frequency during intrathecal use of nonionic monomer contrast media are described. Undesirable effects following intrathecal use may be delayed and present some hours or even days after the procedure. The frequency is similar to lumbar puncture alone.

Headache, nausea, vomiting or dizziness may largely be attributed to pressure loss in the sub-arachnoid space resulting from leakage at the puncture site. Excessive removal of cerebrospinal fluid should be avoided in order to minimise pressure loss.

Psychiatric disorders:

Not known: Confusion, agitation, anxiety, disorientation

Nervous system disorders:

Very common: Headache (may be severe and prolonged)

Uncommon: Aseptic meningitis (including chemical meningitis).

Rare: Seizures, dizziness

Not known: Meningitis, status epilepticus, contrast encephalopathy (see "Description of selected adverse reactions" in section 4.8), motor dysfunction (including speech disorder, aphasia, dysarthria), paraesthesia, hypoaesthesia 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:

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