Imiro™

Iohexol USP

Presentation:
Imiro™ 350 Injection: 37.75 g Iohexol/50 ml equivalent to 350 mg Iodine/ml & 75.5 g Iohexol/100 ml equivalent to 350 mg Iodine/ml

Description:
Iohexol is a nonionic, water-soluble radiographic contrast medium with a molecular weight of 821.14 (Iodine content 46.36%). In aqueous solution each triiodinated molecule remains undissociated. Iohexol is provided as a sterile, pyrogen-free, colorless to pale-yellow solution, in the following iodine concentrations: 350 mgI/mL. All solutions are sterilized by autoclaving and contain no preservatives. Unused portions must be discarded. Iohexol solution is sensitive to light and therefore should be protected from exposure.

Actions:
Iohexol provides opacification of blood vessels and permits radiographic visualisation until sufficient haemodilution occurs or sufficient contrast medium has left the site of injection. Being a non-ionic compound, Iohexol yields solutions of lower osmolality than the conventional ionic contrast media. Intravenous or intra-arterial injection of Iohexol causes less pain and sensation of heat than conventional ionic media with similar iodine content. Iohexol solutions cause less cardiac and vascular disturbances on intravascular injection. The transit time of Iohexol through the coronary vascular system is slightly increased compared with conventional ionic contrast media, probably due to the increased viscosity of Iohexol at comparable iodine concentrations. The period of maximal opacification of the renal vessels may begin as early as 30 seconds after IV injection. Urograms become apparent in about 1 to 3 minutes with optimal contrast occurring between 5 to 15 minutes. In nephropathic conditions, particularly when excretory capacity has been altered, the rate of excretion may vary unpredictably, and opacification may be delayed after injection. Severe renal impairment may result in a lack of diagnostic opacification of the collecting system. The initial concentration and volume of the medium, in conjunction with appropriate patient manipulation and the volume of CSF into which the medium is placed, will determine the extent of diagnostic contrast that can be achieved. Following subarachnoid injection, Iohexol will continue to provide good diagnostic contrast by conventional radiography for at least 30 minutes. Slow diffusion of Iohexol takes place throughout the CSF as well as transfer into the circulation. At approximately 1 hour, contrast of diagnostic quality will not usually be available for conventional myelography. However, sufficient contrast for CT myelography will be available for several hours. If CT myelography is to follow, it should be deferred for several hours to allow the degree of contrast to decrease. Following lumbar subarachnoid placement, irrespective of the position in which the patient is later maintained, slow upward diffusion of Iohexol takes place throughout the CSF. CSF contrast enhancement for CT scanning may be expected in the thoracic region in about 1 hour, in the cervical region in about 2 hours and in the basal cisterns in 3 to 4 hours after administration into the lumbar subarachnoid space.

Pharmacokinetics:
Following intravascular injection, Iohexol is distributed in the extracellular fluid compartment and is excreted unchanged by glomerular filtration. About 87-99% of the injected dose was excreted in the first 24 hours in healthy subjects, depending on age; excretion was less in older subjects. Peak urine concentration occurred in the first hour. The half-life of elimination was 121 to 150 minutes in healthy subjects, again dependant on age. No metabolites were detected in the urine. Binding of Iohexol to human plasma proteins has been measured to be 1.5%. Following injection into the lumbar subarachnoid space, Iohexol is absorbed from CSF into the bloodstream and is eliminated by renal excretion. After lumbar administration of 10-15 ml Iohexol at a concentration of 180 mg I/ml to 6 patients, a mean maximum concentration of 0.024 mg I/ml was observed after a mean of 2.2 hours. The mean half life of the initial rapid distribution phase from blood was 34 minutes and for the slower elimination phase was 3.4 hours.

Indications
Iohexol is an X-ray contrast medium for use in adults and children for cardioangiography, arteriography, urography, phlebography and CT-enhancement. Lumbar, thoracic, cervical myelography and computed tomography of the basal cisterns, following subarachnoid injection. It is also indicated for arthrography, endoscopic retrograde pancreatography (ERP), endoscopic retrograde cholangiopancreatography (ERCP), herniography, hysterosalpingography, sialography and studies of the gastrointestinal tract when the use of barium sulphate is unsatisfactory, undesirable or contraindicated.

Dosage and Administration
The dosage varies depending on the type of examination, age, weight, cardiac output and general condition of the patient and the technique used. Usually the same iodine concentration and volume is used as with other iodinated X-ray contrast media in current use. Adequate hydration should be assured before and after administration as for other contrast media.

The following dosages may serve as a guide.

Indication	Concentration	Volume	Comments
Urography			
adults:	300 mg I/ml	40 - 80 ml	80 ml may be exceeded in selected cases
	or 350 mg I/ml	40 - 80 ml	
children < 7 kg	240 mg I/ml	4 ml/kg	
	or 300 mg I/ml	3 ml/kg	
children > 7 kg	240 mg I/ml	3 ml/kg	
	or 300 mg I/ml	2 ml/kg (max 40 ml)	
Phlebography (leg)	240 mg I/ml or 300 mg I/ml	20 - 100 ml/leg	
Digital subtraction angiography	300 mg I/ml	20 - 60 ml/inj.	
	or 350 mg I/ml	20 - 60 ml/inj.	
CT-enhancemen			
adults:	140 mg I/ml	100 - 400 ml	Total amount of iodine is usually 30 - 60g
	or 240 mg I/ml	100 - 250 ml	
	or 300 mg I/ml	100 - 200 ml	
	or 350 mg I/ml	100 - 150 ml	
Children:	240 mgI/ml	2-3 ml/kg b.w. up to 40ml	In a few cases up to 100 ml may be given
	or 300 mgI/ml	1-3 ml/kg b.w. up to 40ml	

Guidelines for Intra-arterial use

Indication	Concentration	Volume	Comments
Arteriographies			
arch aortography	300 mg I/ml	30 - 40 ml/inj.	Volume per injection depends on the site of injection
selective cerebral	300 mg I/ml	5 - 10 ml/inj.	
aortography	350 mg I/ml	40 - 60 ml/inj.	
femoral	300 mg I/ml	30 - 50 ml/inj.	
	or 350 mg I/ml		
various	300 mg I/ml	depending on type of examination	
Cardioangiography			
adults:			
left ventricle and aortic root inj.	350 mg I/ml	30 - 60 ml/inj.	
selective coronary arteriography	350 mg I/ml	4 - 8 ml/inj.	
children:	300 mg I/ml	depending on age,	
	or 350 mg I/ml	weight and pathology (max 8 ml/kg b.w.)	
Digital subtraction angiography	140 mg I/ml	1 - 15 ml/inj.	depending on site of inj. occasionally large volumes - up to 30 ml - may be used
	or 240 mg I/ml	1 - 15 ml/inj.	
	or 300 mg I/ml	1 - 15 ml/inj.	

Guidelines for Intrathecal use

Indication	Concentration	Volume	Comments
Lumbar and thoracic myelography (lumbar injection)	180 mg I/ml or 240 mg I/ml	10 - 15 ml 8 - 12 ml	
Cervical myelography (lumbar injection)	240 mg I/ml or 300 mg I/ml	10 - 12 ml 7 - 10 ml	
Cervical myelography (lateral cervical injection)	240 mg I/ml or 300 mg I/ml	6 - 10 ml 6 - 8 ml	
CT cisternography (lumbar injection)	180 mg I/ml or 240 mg I/ml	5 - 15 ml 4 - 12 ml	
Paediatric myelography			
<2 years	180 mg I/ml	2 - 6 ml	
2-6 years	180 mg I/ml	4 - 8 ml	
>6 years	180 mg I/ml	6 - 12 ml	

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

Guidelines for Body Cavities:

Indication	Concentration	Volume	Comments
Arthrography			
Adults:	200 mgI/ml	5-20 ml	
	or 240 mg I/ml	5-20 ml	
	or 300 mg I/ml	5-15 ml	
	or 350 mg I/ml	5-10 ml	
ERP/ERCP	240 mg I/ml	20-50 ml	
Herniography	240 mg I/ml	50 ml	The dosage varies with the size of
Hysterosalpingography	240 mg I/ml	15-20 ml	the hernia
	300 mg I/ml	15-20 ml	
Sialography	240 mg I/ml	0.5-2 ml	
	or 300 mg I/ml	0.5-2 ml	
Gastrointestinal Studies			
Oral Use:			
Adults:	180 mg I/ml	Individual	
	or 200 mg I/ml	Individual	
	or 300 mg I/ml	Individual	
Children:	300 mg I/ml	2-4 ml/ kg b.w.	Max. dose 50 ml
-oesophagus	or 350 mg I/ml	2-4 ml/kg b.w.	Max. dose 50 ml
	140 mg I/ml	4-5 ml/ kg b.w.	
-ventricle/follow through			
Prematures	350 mg I/ml	2-4 ml/ kg b.w.	
Rectal Use:			
Children	140 mgI/ml or dilute with tap water to 100-150 mgI/ml	5-10 ml/kg b.w. 5-10 ml/kg b.w.	Example: Dilute Iohexol 240, 300 or 350 with tap-water 1:1 or 1:2
CT-enhancement			
Oral Use:			
Adults	Dilute with tap water to ~6 mg I/ml.	800-2000 ml of the diluted solution over a period of time.	Example: Dilute Iohexol 300 or 350 with tap water 1:50
Children	Dilute with tap water to ~6 mg I/ml.	15-20 mL/kg b.w. of the diluted solution. Individual	
Rectal Use:			
Children	Dilute with tap water to ~6 mg I/ml.		

Contraindications
Manifest thyrotoxicosis. History of serious reaction to Iohexol.

Warnings and Precautions
Special precautions for use of non-ionic monomeric contrast media in general:
A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H1 and H2 antagonists might be considered in these cases. The risk of serious reactions in connection with use of Iohexol is regarded as minor. However, iodinated contrast media may provoke anaphylactoid reactions or other manifestations of hypersensitivity. A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment, should a serious reaction occur. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure. Non-ionic contrast media have less effect on the coagulation system in vitro, compared to ionic contrast media. When performing vascular catheterisation procedures one should pay meticulous attention to the angiographic technique and flush the catheter frequently (e.g.: with heparinised saline) so as to minimise the risk of procedure-related thrombosis and embolism. Adequate hydration should be assured before and after contrast media administration. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction, as well as to infants, small children and elderly patients. Young infants (age < 1 year) and especially neonates are susceptible to electrolyte disturbance and haemodynamic alterations. Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias. Patients with acute cerebral pathology, tumours or a history of epilepsy are predisposed for seizures and merit particular care. Also alcoholics and drug addicts have an increased risk for seizures and neurological reactions. A few patients have experienced a temporary hearing loss or even deafness after myelography, which is believed to be due to a drop in spinal fluid pressure by the lumbar puncture per se. To prevent acute renal failure following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk. Patients with paraproteinemias (myelomatosis and Waldenström's macroglobulinemia) are also at risk.

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

To prevent lactic acidosis, serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium. Normal serum creatinine / renal function: Administration of metformin should be stopped at the time of administration of contrast medium and not resumed for 48 hours or until renal function / serum creatinine is normal. Abnormal serum creatinine / renal function: Metformin should be stopped and the contrast medium examination delayed for 48 hours. Metformin should only be restarted if renal function / serum creatinine is unchanged. In emergency cases where renal function is abnormal or unknown, the physician should evaluate the risk / benefit of the contrast medium examination, and precautions should be implemented: Metformin should be stopped, patient hydrated, renal function monitored and patient observed for symptoms of lactic acidosis. 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. The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis. In patients with phaeochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis. Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goitre may be at risk of developing hyperthyroidism following injection of iodinated contrast media. One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media. Extravasation of contrast media may on rare occasions give rise to local pain, and oedema, 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:
After contrast medium administration the patient should be observed for at least 30 minutes, since the majority of serious side effects occurs within 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.

Use in 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.

Use during Lactation:
Breast feeding may be continued normally when iodinated contrast media are given to the mother.

Effects on Ability to Drive and Use Machines:
It is not advisable to drive a car or use machines during the first 24 hours following intrathecal examination.

Adverse 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. Undesirable effects associated with the use of iodinated contrast media are usually mild to moderate and transient in nature, and less frequent with non-ionic than with ionic contrast media. Serious reactions as well as fatalities are only seen on very rare occasions. The most frequent adverse event is a mild, general sensation such as a feeling of warmth or a transient metallic taste. Abdominal discomfort/pain and gastrointestinal reactions like nausea, vomiting and diarrhoea may occur. Hypersensitivity reactions are rare and usually present as mild respiratory or cutaneous symptoms like dyspnoe, rash, erythema, urticaria, pruritus and angioedema. They may appear either immediately after the injection or up to a few days later. Severe manifestations such as laryngeal oedema, bronchospasm or pulmonary oedema are very rare. Severe and even toxic skin reactions have been reported. Anaphylactoid reactions may occur irrespectively of the dose and mode of administration and mild symptoms of hypersensitivity may represent the first signs of a serious reaction. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the vascular access. Patients using beta-blockers may present with atypical symptoms of anaphylaxis, which may be misinterpreted as a vagal reaction. Vagal reactions giving hypotension and bradycardia are seen on very rare occasions. Headache or fever may occur. Episodes of hypertension may also occur. Pyrexia with rigors is seen on rare occasions. Iodism or "iodide mumps" is a very rare complication of iodinated contrast media resulting in swelling and tenderness of the salivary glands for up to approximately 10 days after the examination.

Intravascular Use (Intraarterial and Intravenous Use):
Please first read the section labelled "General". Below, only undesirable events with frequency during intravascular use of non-ionic monomeric contrast media are described. The nature of the undesirable effects specifically seen during 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. Distal pain or heat sensation in peripheral angiography is common (incidence >1:10).
A transient increase in S-creatinine is common after iodinated contrast media, but usually is of no clinical relevance. Renal failure is very rare. However, renal failure may occur in high risk patients and among such patients fatalities have been reported. Arterial spasm may follow injection into coronary, cerebral or renal arteries and result in transient ischaemia. Neurological reactions are very rare. They may include seizures or transient motor or sensory disturbances. On very rare occasions the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex being visible on CT-scanning until the day following examination, sometimes associated with transient confusion or cortical blindness.
Serious cardiac complications, including cardiac arrest, arrhythmia, depression or signs of ischaemia are very rare. Post phlebographic thrombophlebitis or thrombosis is very rare. A very few cases of arthralgia has been reported. Severe respiratory symptoms and signs (including dyspnoea, bronchospasm, laryngospasm, non-cardiogenic pulmonary oedema) and cough may occur. Thyrotoxicosis may occur. Flushing may occur. Injection site reactions may occur.

Intrathecal use:
Please first read the section labelled "General". Below, only undesirable events with frequency during intrathecal use of non-ionic monomeric 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 are common and may largely be attributed to pressure loss in the subarachnoid space resulting from leakage at the puncture site. Some of these patients may experience a severe headache lasting for several days. Excessive removal of cerebrospinal fluid should be avoided in order to minimise pressure loss. Mild local pain, paraesthesia and radicular pain occasionally (incidence <1:10, but >1:100) occur at the site of injection. Cramping and pain in the lower limbs are seen on very rare occasions. Meningeal irritation giving photophobia and meningism happens occasionally. Frank chemical meningitis appears on very rare occasions. The possibility of infective meningitis should also be considered. On very rare occasions, manifestations of transient cerebral dysfunction are seen. These include seizures, transient confusion or transient motor or sensory dysfunction. Changes in the EEG may be noted in a few of these patients. Transient blindness may occur. Neck pain may occur. Injection site reaction may occur.

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. Systemic hypersensitivity reactions are rare. Endoscopic Retrograde Cholangiopancreatography (ERCP): Some elevation of amylase levels is common. Post ERCP renal opacification is seen on rare occasions and is associated with an increased risk of post ERCP pancreatitis. Rare cases of necrotizing pancreatitis have also been described. Oral use: Gastrointestinal upset occasionally occurs. Hysterosalpingography (HSG): Transient pain in the lower abdomen is common. Arthrography: Post procedural pain is common. Frank arthritis is rare. The possibility of infective arthritis should be considered in such cases. Herniography: Mild postprocedural pain is common.

Interactions:
Use of contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking metformin (see Warnings and Precautions).
Patients treated with interleukin-2 less than two weeks previously have been associated with an increased risk for delayed reactions (flu-like symptoms or skin reactions). 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.

Overdosage:
Preclinical data indicate a high safety margin for Iohexol and no fixed upper dose level has been established for routine intravascular use. Symptomatic overdosing is unlikely in patients with normal renal function unless the patient has received an excess of 2000 mg I/kg body-weight over a limited period of time. The duration of the procedure is important for the renal tolerability of high doses of contrast media (t½ ~ 2 hours). Accidental overdosing is most likely following complex angiographic procedures in children, particularly when multiple injections of contrast medium with high-concentration are given. In cases of overdose, any resulting water or electrolyte imbalance must be corrected. Renal function should be monitored for the next 3 days. If needed, haemodialysis may be used for clearance of excessive contrast medium. There is no specific antidote.

Pharmaceutical Precautions:
Store at room temperature below 30°C and protect from light and secondary X-rays. The product in glass vials and bottles may be stored at 37°C for up to 3 months prior to use.Do not freeze.

Instructions for Use/Handling:
Like all parenteral products, Iohexol should be inspected visually for particulate matter, discoloration and the integrity of the container prior to use. The product should be drawn into the syringe immediately before use. Vials are intended for single use only, any unused portions must be discarded. The 500 ml contrast medium bottles should only be used in connection with auto injectors/pumps approved for this volume. A single piercing procedure should be used.
The line running from the auto injector/pump to the patient must be exchanged after each patient. Any unused portions of the contrast medium remaining in the bottle and all connecting tubes must be discarded at the end of the day. When convenient, smaller bottles can also be used. Instructions from the manufacturer of the auto injector/pump must be followed.

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

Commercial Pack:
Imiro™ 350 Injection: One 50 ml bottle contains Iohexol 37.75 g equivalent to 17.5 g of Iodine at the concentration of 350 mg Iodine/ml.
One 100 ml bottle contains Iohexol 75.5 g equivalent to 35 g of Iodine at the concentration of 350 mg Iodine/ml.

Manufactured by :

POPULAR

POPULAR PHARMACEUTICALS LTD.
TONGI, GAZIPUR, BANGLADESH