SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Iopamiro 300 mg/ml solution for injection
Iopamiro 370 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

	Iopamiro 300 mg/mL Solution for Injection	**Iopamiro 370 mg/mL Solution for Injection**
Active ingredient IOPAMIDOL equal to IODINE	612.4 mg/mL 300.0 mg/mL	755.3 mg/mL 370.0 mg/mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear aqueous solution filled into colourless glass ampoules or bottles.

Iodine concentration	**Iopamidol concentration**	**PH**	**Viscosity cP**		**Density**		**Osmometric values at 37° C**	
mg l/mL	mg l/mL		20° C	37° C	20° C	37° C	Osmolality (osmol.kg^{-1})	Π (atm)
300	612.4	7±0.5	8.8	4.7	1.335	1.328	0.616	15.7
370	755.3	7±0.5	20.9	9.4	1.415	1.405	0.796	20.3

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
X-ray contrast medium in neuroradiology, angiography, urography, CT scanning, arthrography and fistulography.

4.2 Posology and method of administration

Neuroradiology

	Concentration(mg I/ml)	Recommended Dose (ml)
mieloradiculography	300	5 - 15
cisternography and	300	5 - 15

ventriculography		

Angiography

	Concentration (mg I/ml)	Recommended Dosage (ml)
Cerebral arteriography	300	5 - 10 per bolus
Coronary arteriography	370	8 - 15 per bolus
Thoracic aortography	370	1.0 – 1.2/kg
Abdominal aortography	370	1.0 – 1.2/kg
Angiocardiography	370	1.0 - 1.2/kg
Selective visceral arteriography	300-370	depends on the vascular area to be examined
Peripheral arteriography	300-370	40 – 50
Digital Subtraction Angiography	150-370	depends on the vascular area to be examined
Venography (phlebography)	300	30 - 50

Urography

The recommended dosage for this type of investigation is 30-50 ml for adults. The less marked osmotic diuresis induced by the non ionic agent makes Iopamiro® 370 especially suitable for patients with mild or moderately severe renal insufficiency and for neonates. The new contrast medium affords diagnostically useful nephrography even in patients with major renal insufficiency.

OTHER DIAGNOSTIC PROCEDURES

	Concentration (mg I/ml)	Recommended Dosage (ml)
Contrast enhancement in CT scanning	300 - 370	0.5 – 2.0/kg
Artrography	300	depending on examination
Fistulography	300	depending on examination

For the enhancement of contrast in CT scans IOPAMIRO® may be injected intravenously as a bolus, as a drip infusion or by a combination of the two methods.
The administration as an infusion is limited to old generation CT equipment. With spiral CT and the new multislice CT, it is recommended to administer a bolus specially for investigations aiming at increasing contrast enhancement in the arterial phase.
With slow equipment infusion is recommended whilst with fast equipment bolus injection is preferable.

Method of administration

The dosage must be adapted to the examination, the age, body weight, cardiac output, renal function, general condition of the patient and the technique used. Usually the same iodine concentration and volume are used with other iodinated x-ray contrast in current use.

As with all contrast media, the lowest dose necessary to obtain adequate visualisation should be used.

Non-ionic contrast media have less anti-coagulant activity in-vitro than ionic media. Meticulous attention should therefore be paid to angiographic technique. Non-ionic media should not be allowed to remain in contact with blood in the syringe and intravascular catheters should be flushed frequently, to minimise the risk of clotting, which rarely has led to serious thromboembolic complications after procedures.

Factors such as length of procedure, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. Therefore, meticulous angiographic techniques are recommended including close attention to guide wire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions, and minimizing the length of the procedure.

As experience shows that warmed contrast media are better tolerated, the contrast medium should be warmed up to body temperature before administration.

No other drugs or contrast media should be mixed with the iopamidol solution for injection.

Lumbar myelography

A slow sub-arachnoid injection is made through a fine lumbar puncture needle into one of the lower lumbar interspinous spaces (L3-L4 or L4-L5). Optimum contrast appears immediately after injections and films should be obtained promptly.

Thoraco-cervical myelography

Following a slow sub-arachnoid injection the patient should be turned on his side and tilted 10°-20° head down under fluoroscopic control. In this manner it is possible to control movement of the contrast medium column into the dorsal region.

If the cervical region is to be examined, the contrast medium should be run into the cervical region first, before the examination of the dorsal areas where it is progressively diluted.

Iopamiro may also be injected sub-occipitally or by lateral cervical puncture technique. Care should be taken to ensure that the contrast medium does not move intra-cranially.

After completion of direct cervical or lumbo-cervical procedures:
- Raise head of table steeply (45° angle) for about two minutes so that the contrast medium flows towards the caudal end.
- Avoid excessive and particularly active patient movement or straining, maintain the patient under close observation, quiet and in a head up position especially in the first few hours.
- Patients suspected of having a low seizure threshold should be observed during this period.
- The patient should remain supine and at bed rest during this period.
- Encourage the patient, if able, to take in fluids orally and eat.

Cerebral angiography

Any of the current techniques is suitable for radiological visualisation of the cerebral vasculature with Iopamiro 300. Carotid and vertebral angiography, performed by catheterisation or percutaneous injection techniques, require rapid injection, which, if necessary may be repeated.

Peripheral arteriography and phlebography (venography)

Iopamiro may be administered by rapid injection through a catheter into a suitable peripheral artery or vein. Percutaneous injection into the appropriate blood vessel is used for visualisation of peripheral arteries and veins.

Computer tomography enhancement

Contrast enhancement for brain scans can be achieved between one and three minutes after i.v. injection. Iopamiro 300 is also used for total body scanning examinations after i.v. administration as a bolus, as a drip infusion or by a combination of the two methods.

Urography

The contrast medium is injected intravenously and rapidly eliminated through the kidneys. In patients with severe renal failure, high dose urography should be used.

Angiocardiography, left ventriculography, selective coronary arteriography

It can also be introduced under pressure through a cardiac catheter into any of the heart chambers, or injected into large vessels for immediate visualisation. The contrast medium may also be administered during selective catheterisation of the coronary arteries.

Arthrography

Visualisation of joint cavities and articular surfaces can be achieved by either single or double contrast examination.

Digital subtraction angiography

For cardiac imaging the contrast medium may be administered intra-arterially by selective catheterisation to provide subtracted images. Iopamiro 370 injected intravenously either centrally or peripherally is also recommended for use in this modality.

4.3 Contraindications

Hypersensitivity to the active substance and the water-soluble contrast media or to any of the excipients listed in section 6.1.

Intrathecal administration

The concomitant intrathecal administration of corticosteroids with Iopamidol is contraindicated (see section 4.5 Interaction with other medicinal products and other forms of interaction).
Because of overdosage considerations, immediate repeat myelography in the event of technical failure is contraindicated.

4.4 Special warnings and special precautions for use

Exceptionally, crystals can be detected in an Iopamiro package. This is due to a damaged or otherwise imperfect carton box and therefore the use of this package is not recommended.
The use of organic iodinate contrast media should be limited to cases for which there is a precise need for contrastographic examination.

Diagnostic procedures which involve the use of any radiopaque medium should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed.
Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reaction to the contrast medium itself.

As with all other contrast media this product may provoke anaphylaxis or other manifestations of allergy with nausea, vomiting, dyspnoea, erythema, urticaria and hypotension. Occasional severe reactions with fatal outcome have been reported.

A positive history of allergy, asthma or untoward reaction during previous similar investigations indicates a need for extra caution; the benefit should clearly outweigh the risk in such patients.

After administration of the contrast medium, the risk of reactions that may induce bronchospasm is greater in asthmatic patients, particularly in patients who are taking beta blockers.

Pre-treatment with antihistamines or corticosteroids to prevent or minimize possible allergic reactions in such patients may be considered.

During the examination an intravenous route for emergency treatment in the event of severe reactions is required.

After the administration of the contrast medium, competent personnel, drugs and equipment for emergency resuscitation must be available. All patients should be observed for at least 30 minutes.

Contrast media designed for angiocardiographic procedures should be used in hospitals or clinics equipped and staffed for intensive care in emergencies.
For other more common diagnostic procedures calling for the use of iodinated contrast media, in the radiology departments of public or private clinics, where such procedures are to take place, resuscitation equipment and therapeutic measures should be immediately available (AMBU, oxygen, antihistaminic, vasoconstrictors, cortisonics, etc.).

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed haemodynamic disturbances, which may be associated with a transitory increase in the circulating osmotic load.

The patient should also be informed that allergic reactions may develop up to several days after the procedure; in such case, a physician should be consulted.

Extreme caution during injection of contrast media is necessary to avoid extravasation.
Local tissue irritation can occur in the case of perivascular infiltration of the contrast media.

Patients must be sufficiently hydrated before and after radiographic procedures. Patients with severe functional impairment of the liver or myocardium, myelomatosis, diabetes, polyuria or oliguria, hyperuricemia, infants, elderly patients and patients with severe systemic disease should not be exposed to dehydration.

Fluid intake should not be limited and any abnormalities of fluid or electrolyte balance should be corrected prior to use of this hypertonic solution.

Particularly fluid intake should not be limited in infants and young children, and also any abnormalities of fluid or electrolyte balance should be corrected prior to use of hypertonic contrast media.

In patients who are known epileptics or have a history of epilepsy, anticonvulsant therapy should be maintained. In some instances anticonvulsant therapy may be increased for 48 hours before the examination.

The risk associated with a particular investigation may be increased by conditions such as advanced arteriosclerosis and hypertension.

Conditions exposing to a greater risk of serious adverse events
In all the following conditions, due to the increased risk of serious adverse events, a careful evaluation of the risk-benefit ratio is recommended prior to treatment.

Patients with increased risk include those for which there is a suspicion of previous reactions to contrast or iodinated media and those suffering from allergic diseases (bronchial asthma, hay fever or food allergies).

Patients with paraproteinaemia of Waldenström, with multiple myeloma or severely compromised hepatic and renal impairment are also at special risk; these patients should be adequately hydrated.

To prevent crises in patients with sickle cell disease adequate hydration should be assured and a minimal volume of low concentration should be used.

Care should be exercised in patients with moderate to severe impairment of renal function.

In patients with impaired renal function, administration of contrast media can cause episodes of acute renal failure.
Key preventive measures include identification of high-risk patients, ensuring adequate hydration prior to contrast agent administration, preferably maintaining the intravenous infusion before and during the procedure, until the contrast medium has not been eliminated by kidneys; avoid administration of nephrotoxic drugs or undergoing the patient to major surgery or procedures such as renal angioplastic, until the contrast medium has not been completely eliminated by the kidneys; monitor renal function parameters after the procedure; postpone a new examination with contrast medium until the return of renal function to pre-examination levels.

Patients with severe hepatic, renal or combined hepato-renal insufficiency should not be examined unless absolutely indicated.
Re-examination should be delayed for 5-7 days.

Patients on dialysis may receive contrast media such as Iopamiro, which can be removed without difficulty by dialysis.

The presence of renal damage in diabetic patients is one of the factors predisposing to acute renal impairment following intravascular contrast media administration. This may precipitate lactic acidosis in patients who are taking biguanides (see section 4.5).

Caution should be exercised in performing iodinated contrast-enhanced examinations in patients with, or with suspicion of, hyperthyroidism or autonomously functioning thyroid nodule(s), as thyroid storms have been reported following administration of iodinated contrast media.

It is possible that hyperthyroidism may recur in patients previously treated for Graves' disease.

In patients with hyperthyroidism, the radiological examination should be performed only if thought necessary by the physician.
In patients scheduled for thyroid examination and/or treatment with a radioactive iodine tracer, iodine update in the thyroid gland will be reduced for several days, sometimes up to 2 weeks after dosing with an iodinated contrast medium that is eliminated through the kidneys.
Use of this product might interfere with tests for thyroid function.

Patients with phaeochromocytoma can develop severe hypertensive crises following intravascular iopamidol administration. Premedication with α receptor blockers is recommended.

Contrast induced encephalopathy

Encephalopathy has been reported with the use of iopamidol (see section 4.8). This may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema within minutes to hours after administration and generally resolves 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.
If contrast encephalopathy is suspected, iopamidol should not be re-administered and appropriate medical management should be initiated.

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

Iopamidol should be administered with caution in patients with hyperkalaemia and cerebral vascular disease.

Iopamidol should be administered with caution in patients with symptomatic cerebrovascular disease, heart attack/recent stroke or transient ischemic attack (TIA), abnormal permeability of the blood-brain barrier, increased intracranial pressure, suspicion of intracranial tumour, abscess or hematoma/haemorrhage, previous seizures, alcoholism.

Neuroradiology

The contrast medium should be removed as much as possible in case of spinal fluid blockage.Patients receiving treatment with anticonvulsant drugs must continue such treatment before and after the procedure.
Should a convulsive seizure develop during the examination, administer diazepam or sodium phenobarbital intravenously.

Intrathecal administration
An accurate evaluation of the risk/benefit ratio is needed if from clinical history there is a previous history of epilepsy or in the presence of blood in the cerebrospinal fluid or presence of local or systemic infection where bacteraemia is likely.
The operator should evaluate in those cases the diagnostic need against possible risk to the patient.
After completion of direct cervical or lumbo-cervical procedures: see in section 4.2

Angiography
The risk associated with a particular investigation may be increased by conditions such as advanced arteriosclerosis, hypertension, heart failure, severe systemic disease, embolism or recent cerebral thrombosis.

In patients undergoing angiocardiographic procedures special attention should be paid to the status of the right heart and pulmonary circulation. Right heart insufficiency and pulmonary hypertension may precipitate bradycardia and systemic hypotension, when the organic iodine solution is injected. Right heart angiography should be carried out only when absolutely indicated.

During intracardiac and/or coronary arteriography, ventricular arrhythmias may infrequently occur.

Great caution should be paid when injecting the contrast medium into the heart chambers, especially in cyanotic neonates with pulmonary hypertension and impaired cardiac function.

The intravascular injection of a contrast medium can evolve in pulmonary oedema in patients with congestive heart failure.

In angiographic procedures, the possibility of dislodging plaque or damaging or perforating the vessel wall should be considered during catheter manipulation and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

In examinations of the aortic arch, the tip of the catheter should be positioned carefully to avoid hypotension, bradycardia and CNS injury due to excess pressure transmitted from the injector pump to the brachiocephalic branches of the aorta.

Angiography should be avoided whenever possible in patients with homocystinuria due to an increased risk of thrombosis and embolism.

Vasospasm and subsequent cerebral ischemic phenomena may be caused by intra-arterial injections of contrast media.

Even in abdominal angiography excessive pressure transmitted by the automatic pump can cause renal infarction, spinal cord injury, retroperitoneal haemorrhage, myocardial and intestinal necrosis.

In peripheral arteriography using Iopamiro 370 mg/mL Solution for injection can cause the onset of painful effects that are not manifest with Iopamiro 300 mg/mL Solution for injection.

In patients undergoing peripheral angiography, the pulsation of the artery in which the contrast medium should be injected needs to be appreciated. In patients with thromboangiitis obliterans, or ascending infections in association with severe ischemia caution should be exercised in performing angiography, if necessary.
In patients undergoing venography, special caution should be exercised in patients with suspected phlebitis, serious ischemia, local infections, or a complete venous occlusion.

It has been shown in vitro that the inhibitory effects of non-ionic contrast media on the mechanisms of haemostasis are lower than those of ionic contrast media at the same concentration.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), such Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (Lyell's syndrome or TEN) and acute generalised exanthematous pustulosis (AGEP), which can be life threatening, have been reported in patients administered with Iopamiro (see section 4.8, undesirable effects). At the time of initiation, patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If signs and symptoms suggestive of these reactions appear, further use of Iopamiro should be withheld. If the patient has developed a severe cutaneous adverse reaction with the use of Iopamiro, Iopamiro must not be re-administered in this patient at any time.

Use in Special Populations
Newborns, children **-** Infants (age<1 year), and especially newborns are particularly susceptible to electrolyte imbalances and haemodynamic alterations. Care should be taken regarding the dosage to be used, the details of the procedure, and the patient's status.

Transient thyroid suppression or hypothyroidism has been observed in children after exposure to iodinated contrast media.
Following a diagnostic procedure, this has been more frequently observed in neonates and premature infants and also following procedures associated with higher doses. Neonates may also be exposed via maternal exposure.
In neonates, especially preterm infants, who have been exposed to iopamidol, either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function.
If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalised.

Elderly **-**The elderly are at special risk of reactions due to reduced physiological functions, especially when high dosage of contrast medium is used. Myocardial ischemia, major arrhythmias and premature ventricular complexes are more likely to occur in these patients. The probability of acute renal insufficiency is higher in these patients.

Women of child-bearing potential - Appropriate investigations and measures should be taken when exposing women of child-bearing potential to any X-ray examination, whether with or without contrast medium (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

To prevent onset of lactic acidosis in diabetic patients under treatment with oral anti-diabetic agents of the biguanide class, biguanides should be stopped 48 hours before the administration of the contrast medium and re-instated only after renal function has been demonstrated to have returned to pre-examination values (see section 4.4).

In emergency patients in whom renal function is either impaired or unknown, the physician shall weigh out risk and benefit of an examination with a contrast medium.

Metformin should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

Patients with normal renal function can continue to take Metformin normally.

Cardiac and/or hypertensive patients under treatment with diuretics, ACE-inhibitors, and/or beta-blocking agents are at higher risk of adverse reactions when administered iodinated contrast media.

Following administration of iopamidol atypical adverse reactions e.g. erythema, fever and flu symptoms have been reported in patients treated with interleukin-2 and interferon.

Following administration of iopamidol, the capacity of the thyroid tissue to take up iodine is reduced for 2-6 weeks.
Arterial thrombosis has been reported when iopamidol was given following papaverine. The administration of vasopressors strongly potentiates the neurological effects of intra-arterial contrast media.

Renal toxicity has been reported in patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents.
However, recent studies have not shown interactions of contrast agents excreted by the kidney with oral cholecystographic contrast agent.

Contrast media may interfere with laboratory tests for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium, and phosphate). These substances should not be assayed during the same day following the administration of contrast media.

In patients receiving beta-blockers there is an elevated risk of more severe anaphylactoid reactions.

Beta-blockers may impair the response to treatment of bronchospasm induced by contrast medium.

Intrathecal administration
Intrathecal corticosteroids should never be concurrently administered when Iopamidol is used (see Section 4.3).
Neuroleptics should be avoided as they lower the seizure threshold. This is also true for drugs such as analgesics, antiemetics, antihistaminics, or sedatives of the phenothiazine group.
Wherever possible the therapy with such drugs must be discontinued at least 48 h before the radiological investigation and treatment can be resumed not earlier than 24 h afterwards.
Alcoholism or drug addiction increase the permeability of the blood brain barrier. This facilitates the passage of iodinated agents in brain tissue with possible CNS disorders. A possible lowering of seizure threshold should be kept in mind.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of iopamidol injection during pregnancy has not been established.

Since radiation exposure during pregnancy should be avoided anyway, regardless of whether a contrast agent is used or not, the benefit of X-ray examination has to be considered carefully. Apart from radiation exposure of the foetus, benefit-risk consideration for iodine-containing contrast agents should also take into account the sensitivity of the foetal thyroid towards iodine (see section 4.4).

Animal studies do not indicate direct or indirect effects on pregnancy and embryonal/fetal development. Caution is needed in prescribing the contrast medium in pregnant women.

Lactation
Iodine-containing X-ray contrast agents are excreted into the breast milk in low amounts. At therapeutic doses harmful effects on the nursing infant are unlikely. However, although no side effects in nursing infants have been reported, caution should be exercised when administering endovascular X-ray contrast media to nursing women because of potential adverse events and discontinuation of breastfeeding for 24 hours after treatment with iodinated contrast should be considered.

Fertility
There are no adequate and controlled clinical trials on fertility.

4.7 Effects on ability to drive and use machines

There is no available data on Iopamiro effects on the ability to drive and operate machines. Before driving or operating machinery, side effects such as hypotension, dizziness, confusion, shortness of breath, which may occur with the use of this medicinal product, should be taken into account.
Driving or operating machinery is not advisable for 6 hours following intrathecal administration.

4.8 Undesirable effects

The use of iodinated contrast media may cause untoward side effects.
Side effects are usually mild to moderate and transient in nature; however, rare severe and life-threatening reactions, sometimes leading to death, have been reported.

Following intravascular administration, in most cases reactions occur within minutes of dosage. However, delayed reactions, usually involving skin, may occur, mostly within 2-3 days, more rarely within 7 days, after the administration of the contrast medium.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with Iopamiro administration (see section 4.4).

After intrathecal administration, most side effects occur with a delay of some hours due to the slow absorption from the site of administration and distribution to the whole body. Reactions usually occur within 24 hours after injection.

More severe reactions affecting the cardiovascular system, such as marked hypotension, tachycardia, dyspnoea, agitation, cyanosis and loss of consciousness, may require emergency measures.

The adverse reactions reported in clinical trials among 3,008 adult subjects and 35 paediatric patients, and from post marketing surveillance are presented in the tables below by frequency and classified by MedDRA system organ classes.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Intravascular administration
Adult subjects
Adult patients involved in clinical trials with intravascular administration of Iopamidol were 2,919, of whom 1,681 with intra-arterial and 1,238 with intravenous administration.

System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Frequency unknown***
Blood and lymphatic system disorders				Thrombocytopenia
Metabolism and nutrition disorders				Acidosis, Anorexia
Immune system disorders				Anaphylaxis, Anaphylactoid reactions
Psychiatric disorders			Confusional state	

Nervous system disorders	Headache	Dizziness, Taste alteration	Paraesthesia	Coma, Transient ischaemic attack, Syncope, Depressed level of consciousness or loss of consciousness, Convulsion, Amnesia, Paralysis, Sleepiness, Tremors, Hemiplegia, Contrast induced encep halopathy***
Eye disorders				Transient blindness Visual disturbance, Conjunctivitis, Photophobia, Ocular itching, Increased tear secretion
Ear and labyrinth disorders				Auditory deficit
Cardiac disorders		Cardiac dysarrhythmias such as extrasystoles, Atrial fibrillation, Ventricular tachycardia and ventricular fibrillation**	Bradycardia	Cardiopulmonary arrest, Myocardial ischemia or infarction, Heart failure, Angina pectoris, Cyanosis, Tachycardia, Kounis syndrome
Vascular disorders		Hypotension, Hypertension, Redness		Circulatory collapse or shock, Thromboembolismus, Arterial thrombosis, Venous thrombosis Thrombophlebitis, Pallor
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema, Asthma, Bronchospasm	Respiratory arrest, Apnoea, Respiratory failure, Acute respiratory distress syndrome, Laryngeal oedema, Dyspnoea, Coughing, Rhinitis, Sneezing
Gastrointestinal disorders	Nausea	Vomiting, Diarrhea, Abdominal pain, Dry mouth		Salivary gland enlargement, Salivary hypersecretion

Skin and subcutaneous tissue disorders		Rash, Urticaria, Pruritus, Erythema, Hyperhidrosis		Facial oedema, Periorbital oedema, Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		Back pain	Muscle spasms	Musculoskeletal pain, Muscular weakness
Renal and urinary disorders		Acute renal failure		Anuria, Urinary retention, Renal failure (including acute renal failure and renal damage), Oliguria, Hematuria, Urinary incontinence
General disorders and administration site conditions	Feeling hot	Chest tightness pain, Injection site pain, Pyrexia, Feeling cold		Rigors, Pain, Malaise
Investigations		Blood creatinine increased		Electrocardiogram change (including ST segment depression, increased T-wave amplitude, prolonged QT), Decreased systolic blood pressure, Electrolyte imbalances

* Frequency cannot be estimated from the available data.

** Cardiac dysarrhythmias may occur mostly after cardiac angiographic and coronary catheterization procedures.
*** Contrast induced encephalopathy may manifest with symptoms and signs described in section 4.4

The most appropriate MedDRA term is used to describe a certain reaction, its symptoms and related conditions.

Coronary thrombosis has been reported as a complication of coronary catheterization procedures.

Accidents during the procedure could lead to pseudoaneurysm and/or peripheral embolism or cause bruising at the site of administration.

Brachial plexus injury can occur due to axillary artery injection.

Other cardiac reactions which may occur as a consequence of the procedural hazard include coronary artery dissection.

Anaphylaxis (anaphylactoid reactions/hypersensitivity) may manifest with: localized or diffuse angioneurotic oedema, tongue oedema, laryngospasm or laryngeal oedema, dysphagia, pharyngitis and throat tightness, pharyngolaryngeal pain, cough, conjunctivitis, rhinitis, sneezing, feeling hot, sweating increased, asthenia, dizziness, pallor, dyspnoea, wheezing, bronchospasm, and moderate hypotension.
Skin reactions may occur in the form of various types of rash, redness, diffuse blisters, urticaria, and pruritus. These reactions, which occur irrespective of the dose administered and the route of administration, may represent the first signs of incipient state of shock. Administration of the contrast medium must be discontinued immediately and – if necessary – specific treatment initiated via a venous access.
More severe reactions involving the cardiovascular system such as redness with severe hypotension, tachycardia, dyspnoea, agitation, cyanosis and loss of consciousness (syncope) may result in respiratory and/or cardiac arrest. These reactions may occur rapidly and require emergency treatment.
A cardiovascular collapse can occur as the only and/or initial presentation without respiratory symptoms or without other signs or symptoms.

Injection site pain and swelling may occur. On very rare occasions extravasation of contrast medium led to inflammation, skin necrosis and compartment syndrome.

Severe skin diseases
As with other contrast media, very rare cases of mucocutaneous syndromes, including Stevens- Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome) and erythema multiforme, have been reported following the administration of Iopamidol.

Paediatric patients
The iopamidol safety profile is similar in children and adults.

Cases of transient neonatal hypothyroidism have been reported with Iopamidol in very low birth weight infants.

Intrathecal administration

Adult subjects
Adult patients involved in clinical trials with intrathecal administration of Iopamidol were 132.

	Adverse Reactions			
	Clinical Trials			**Post-marketing Surveillance**
System Organ Class	**Very common (≥ 1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Frequency unknown***
Infections and infestations				Meningitis aseptic, Meningitis bacterial as consequence of the procedural

				hazard
Metabolism and nutrition disorders				Acidosis
Immune system disorders				Anaphylaxis, Anaphylactoid reactions
Psychiatric disorders				Hallucinations, Confusion, Disorientation, Depression, Agitation, Anxiety, Irritability
Nervous system disorders	Headache			Coma, Syncope, Depressed level of consciousness or loss of consciousness, Seizures, Paralysis, Myelitis, Meningism, Vertigo, Paraesthesia, Hypoaesthesia Dizziness, Radicular pain, Drowsiness, Tremors, Muscle spasms, Contrast induced encephalopathy**
Eye disorders				Transient blindness, Conjunctivitis, Photophobia, Increased tear secretion, Itchy eyes
Ear and labyrinth disorders				Auditory deficit, Tinnitus

Cardiac disorders				Arrhythmia, Tachycardia, Cyanosis
Vascular disorders		Redness		Hypertension
Respiratory, thoracic and mediastinal disorders				Respiratory arrest, Apnoea, Respiratory Failure, Dyspnoea
Gastrointestinal disorders		Nausea, Vomiting		
Skin and subcutaneous tissue disorders			Rash, Hyperhidrosis	
Musculoskeletal and connective tissue disorders		Back pain, Neck pain, Pain in extremity, Sensation of heaviness		Muscular weakness
Renal and urinary disorders				Renal failure (including acute renal failure), Urinary retention, Hematuria, Urinary incontinence
General disorders and administration site conditions				Pyrexia, Malaise, Rigor

* Frequency cannot be estimated from the available data.
** Contrast induced encephalopathy may manifest with symptoms and signs described in section 4.4

The most appropriate MedDRA term is used to describe a certain reaction, its symptoms and related conditions.

Anaphylaxis (anaphylactoid reactions/hypersensitivity) may occur.
Anaphylactoid reactions with circulatory disturbances such as severe blood pressure decrease leading to syncope or cardiac arrest and life threatening shock are much less common after intrathecal administration than after intravascular administration. Also less common than after intravascular administration are the respiratory (dyspnoea or respiratory distress in the form of bronchospasm) and mucocutaneous reactions (urticaria, angioneurotic oedema and other skin reactions such as rash).

Urography
Side effects that may arise in connection with intravenous urography are as described at the beginning of the paragraph.

Paediatric patients
The iopamidol safety profile is similar in children and adults.
Cases of transient neonatal hypothyroidism have been reported with Iopamidol in very low birth weight infants.

Use in body cavities
The majority of the reactions occur some hours after the contrast administration due to the slow absorption from the area of administration and distribution in the whole organism.

Very rare cases of pancreatitis have been described.

The reactions reported in cases of arthrography and fistulography usually represent irritative manifestations superimposed on existing tissue inflammation.

Systemic hypersensitivity is rare, generally mild and in the form of skin reactions. However, the possibility of severe anaphylactoid reactions cannot be excluded.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Most side effects (see Section 4.8) are not dose-dependent and may therefore require therapeutic interventions as specified in Section 4.4.
In the event of voluntary or accidental administration of higher than normal doses, excretion should be facilitated by ensuring patient hydration, as clearance almost totally occurs via the kidney. In the event of renal insufficiency, whether pre-existing or manifesting after contrast medium introduction, dialysis will eliminate the contrast medium.

Dosages exceeding the specific doses as recommended in section 4.2 “Posology and method of administration”, are **not recommended**, as they might lead to life-threatening adverse effects.

If needed, haemodialysis can be used to eliminate iopamidol from the body.

Treatment of overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Intravascular administration

In the event of accidental intravascular overdose, the water and electrolyte losses must be compensated by infusion. Renal function should be monitored for at least three days.

Intrathecal administration
Signs of intrathecal overdose may be: ascending hyperreflexia, tonic-clonic spasms, up to sudden seizures, and, in severe cases of central involvement, hyperthermia, stupor and respiratory depression.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: Iodated, X-ray contrast media: Water-soluble, nephrotropic, low osmolar X-ray contrast media.
ATC code: V08AB04
Iopamidol is a non-ionic radio-opaque hydrosoluble substance with strongly reduced toxicity and no teratogenic effects. Its use at doses 2 to 4 times higher than for clinical use provoked transient bradycardia and hypotension in dogs, followed by mild hypertension and increased respiratory frequency.
Base values were returned to in 2-4 minutes.
The results of a prospective study with CT multilayer method indicate that the incidence of contrast nephropathy in patients with moderate or severe renal insufficiency (creatinine clearance between 10:59 mL/min/1.73m^2) undergoing TC examination after intravenous administration of a dose equal to 40 g of iodine, was low and not significantly different with the nonionic monomer at low osmolality, iopamidol and with a nonionic iso-osmolar dimer. With iopamidol no cases of increased serum creatinine more than or equal to 0.5 mg/dL has been recorded, iopamidol and nonionic dimer caused increases in serum creatinine more than or equal to 25% of baseline values in the 3.9-4.0% of treated patients.
The incidence of contrast nephropathy in patients undergoing cardioangiographic investigations with iopamidol is similar to that observed after administration of a nonionic iso-osmolar dimer.

5.2 Pharmacokinetic properties

Metabolism: In humans and animal iopamidol does not undergo detectable metabolic processes.
Excretion: the vast majority is via renal route.
In dogs, 93-95% of the administered dose was excreted renally and 0.5% through the biliary route in 7-10 hours.
In humans, more than 90% of the dose is excreted by the urinary route in 24 hours.
Blood half-life in the excretion phase (T ½ B) is approximately 60 minutes in doges and 90-120 minutes in humans.

For intrathecal administration it will pass into the bloodstream, with peak reached in 90-150 min. and almost complete excretion in 24 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients are: trometamol, hydrochloric acid, calcium disodium edetate, water for injections.

6.2 Incompatibilities

Contrast media must not be mixed with other medicinal products, except for heparin.

6.3 Shelf life

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

6.4 Special precautions for storage

Protect from light.

6.5 Nature and contents of container

Colorless Type I glass vials or bottles.

Pack sizes:

Iopamiro 300: 50, 100, or 200 ml of solution.

Iopamiro 370: 50, 100, or 200 ml of solution.

Not all pack sizes maybe marketed.

6.6 Special precautions for disposal and other handling

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

The bottle, once opened, must be used immediately.

Iopamiro, as other iodinated contrast media, can react with metallic surfaces containing copper (e.g. brass), therefore the use of equipment, in which the product comes into direct contact with such surfaces, should be avoided.

7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER

Iopamiro 300: 020 40 24483 11
Iopamiro 370: 020 41 24526 11

Revised in March 2023 according to MOH guidelines.