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Guideline on core SmPC and Package Leaflet for iopamidol 300

Draft

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Guideline on core SmPC and Package Leaflet for iopamidol 300

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Executive summary

This guideline describes the information to be included in the Summary of Products Characteristics (SmPC) and package leaflet for iopamidol 300.

1. Introduction (background)

This core SmPC has been prepared on the basis of national SmPCs, and taking into account the published scientific literature. Any marketing authorisation application or variation of a marketing authorisation for a diagnostic medicinal product containing iopamidol 300 should be accompanied by the required data and documents for the application to be valid.

The indications in section 4.1 are provided as clinical settings sufficiently documented at the time of publication of this core SmPC. However, this list of clinical settings does not waive the need to submit the required studies to support the claimed indication or an extension of indication.

2. Scope

This core SmPC and package leaflet covers iopamidol 300.

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

4. Core SmPC and Package Leaflet for iopamidol 300

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{X} 300 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 612.4 mg iopamidol, equivalent to 300 mg iodine
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless or light yellow solution

pH		[Product specific]
Osmolality at 37 °C [mOsm/kg H2O]		[Product specific]
Osmolarity at 37 °C [mOsm/kg H2O]		[Product specific]
Viscosity [mPa s]	20 °C	[Product specific]
	37 °C	[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Iopamidol 300 mg/ml solution is a radiographic contrast medium indicated for visualisation of abnormal structures or lesions and differentiation between healthy and pathological tissue in arteriography, angiocardiography, phlebography, intravenous digital subtraction angiography (i.v. DSA) and computertomography (CT), excretory urography.

4.2 Posology and method of administration

Posology

Adults, adolescents and children

The dosage is dependent on the method of examination, the age, body weight, cardiac output, general condition of the patient as well as the technique used. The lowest dose necessary to obtain adequate visualisation should be used.
The following dose recommendations are based on general experience with non-ionic x-ray contrast media as well as clinical studies performed with iopamidol. The total volume applied should not exceed 250 ml.

Intra-arterial use

	Adults	Children
Cerebral Arteriography (non-selective)	Sheet film angiography: 40-60 ml Digital subtraction angiography: 20 – 30 ml.	The dosage depends on the body weight and

		age.
Cerebral Arteriography (selective)	Sheet film angiography: 4-12 ml Digital subtraction angiography: 3 – 8 ml	
Pulmonary arteriography	Digital subtraction angiography 25 ml per single injection; overall dose up to 170 ml	
Other regions	Sheet film angiography: The volume of the single injection depends on the vascular region to be examined. Maximum of 250 ml. Digital subtraction angiography 30 – 50 ml. The volume of the single injection depends on the vascular region to be examined. Maximum of 250 ml.	
Angiocardiography	The volume of the single injection depends on the vascular region to be examined. Maximum of 250 ml.	The dosage depends on the body weight and age.
Coronary angiography	4 - 10 ml/artery, to be repeated if required	

Intravenous administrationuse

	Adults	Children
Phlebography	50 ml, depending on body weight and age	
Intravenous digital subtraction angiography (i.v. DSA)	30 - 50 ml, to be repeated if required	The dosage depends on the body weight and age.
Computer tomography (CT)	1 – 2 ml/kg body weight	The dosage depends on the body weight and age.
Excretory urography	50-100 ml	0 – 1 month 4 - 5-(6) ml/kg 1 – 3 month 4 ml/kg 3 – 6 month 3.5 - 4 ml/kg 6 – 12 month 3 – 3.5 ml/kg 12 – 24 month 2.5 - 3 ml/kg 2 – 5 years 2.5 ml/kg 5 – 7 years 2 – 2.5 ml/kg 7 – 12 years 1.5 – 2 ml/kg

The maximum dose for iopamidol with 300 mg Iodine/ml is 2 ml/kg bodyweight.

Special populations

Children

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

Renal impairment/hepatic impairment

In impaired renal function, cardio-circulatory insufficiency as well as bad general condition, the dosage of contrast media should be kept as low as possible (see section 4.4). In these patients it is advisable to monitor renal function at least three days following the examination. Particular caution is required in patients with concomitant hepatic insufficiency and renal insufficiency, which increases the risk of retention of the contrast agent.

Elderly (aged 65 years and above)

No dosage adjustment is considered necessary. Caution should be exercised in elderly patients (see section 4.4).

Method of administration

For intravenous and intra-arterial injection and infusion. A bolus injection is possible.

The contrast medium should be warmed to body temperature before administration for better tolerability and ease of injection as viscosity will be reduced.

The contrast medium should be drawn in the syringe immediately before use. To minimise the risk of clotting, which rarely has led to serious thromboembolic complications after procedures, non-ionic contrast media should not be allowed to remain in contact with blood in the syringe and intravascular catheters should be flushed frequently. 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.

The contrast medium should be applied in the supine patient. Immediate repositioning must be possible.

Caution during injection of contrast media is necessary to avoid extravasation. 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.

Peripheral arteriography and phlebography
Percutaneous injection into the appropriate blood vessel is used for visualisation of peripheral arteries and veins.

Angiocardiography, left ventriculography, selective coronary arteriography
Iopamidol may be administered by rapid injection through a catheter into a suitable peripheral artery or vein. 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.

Aortography
The contrast medium may be introduced directly by intra-arterial injection (retro-grade method) for visualisation of the aorta and its main branches.

Selective visceral angiography
Visualisation can be achieved by selective catheterisation and injection into the hepatic, coeliac or mesenteric arteries.

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

Excretory 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. In intravenous urography it has to be considered that the physiologically low concentration capacity of the immature nephron of children's kidneys requires relatively high doses of contrast media.

Computer tomography (CT)
The product can be administered by rapid intravenous injection, if available, by using an injector. It can also be injected by a slow infusion by hand, in particular for enhancement of the central nervous system where 5 to 10 min waiting time is necessary before taking the images. In spiral CT, especially when using multi-slice technique, a multitude of information is captured while breath is held. In order to optimize the effect of the intravenous bolus injection in the examined region (time-dependent accumulation in the single pathologically altered tissues), the use of an automatic high pressure injector and the bolus administration are recommended.

The doses and delivery rate of contrast media for CT depend on the organs to be examined, on the diagnostic problem and especially on the device available (e. g. scan and image build-up times). For slow-processing devices administration by infusion is recommended, for rapid scanners bolus injection is recommended.

If this medicinal product is intended to be used with an automatic administration system, its suitability for the intended use has to be demonstrated by the manufacturer of the medical device. Instructions for use of the medical device must be followed absolutely. In infants and toddlers automatic administration systems must not be used.

This medicinal product is for single use only. Multiple injections or repeated examinations are possible.

4.3 Contraindications

Previous anaphylactic reaction to iodine, to the active substance iopamidol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

<u>General Warnings</u>

- Iodinated contrast media should only be used after precise clinical indication considering possible risk factors of the examined patient. Strict indication and special care is required in patients with
- known allergic disposition
- latent thyrotoxicosis, euthyroid goiter
- renal impairment in particular in combination with severe liver dysfunction.
- severe cardiovascular disease
- bronchial asthma
- diabetes mellitus
- cerebral convulsive disorder
- advanced cerebral atherosclerosis
- acute cerebral infarction

- acute intracranial bleeding or conditions accompanied by impairment of the blood-brain barrier and cerebral oedema
- bad general condition, dehydration
- dys- or paraproteinaemia
- phaeochromocytoma

Hypersensitivity

As with other iodinated contrast media, iopamidol can be associated with anaphylactoid/ hypersensitivity or other idiosyncratic reactions. Usually these reactions become manifest as minor respiratory or cutaneous symptoms, such as mild difficulties of breathing, skin reddening (erythema), urticaria, pruritus or facial oedema. Most of these reactions occur within half an hour of administration, but in rare cases delayed reactions (after hours or days) may occur. Severe anaphylactic reactions, including shock, occur very rarely, are immediate and can lead to death. They are independent of the dose, may occur upon the first administration of the product, and are often unforeseeable. The risk of a major reaction makes it necessary to have immediate access to the resources necessary for emergency treatment.

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 including skilled personnel with sufficient medical experience as well as medication and equipment for emergency resuscitation. All physicians and nursing staff must be informed of adverse reactions as well as general and medicinal emergency measures:

Before administration of the contrast medium
- at-risk patients should be identified by taking a detailed past history: ask the patient about previous reactions to contrast media or allergies. Patients with either previous reaction to contrast media, history of bronchial asthma or other allergic disposition, have an increased risk of hypersensitivity reactions.
- premedication with antihistamines and/or glucocorticoids in patients with the highest risk / known intolerance should be considered. However, they cannot prevent the occurrence of serious or fatal anaphylactic shock.
- Pretesting using a low dose of contrast medium for hypersensitivity is not recommended, as this is not meaningful and occasionally resulted in serious, sometimes fatal hypersensitivity reactions.

During the investigation
- supervision by a physician should be provided
- The insertion of a flexible in-dwelling catheter is recommended during the entire examination. To permit immediate emergency countermeasures, medication (e.g. epinephrine and antihistamines) and an endotracheal tube and a respirator for the treatment of hypersensitivity reactions must be ready for use.

After administration of the contrast medium
- the patient should be kept under supervision for at least 30 minutes since the majority of serious adverse effects occur within this time.
- if hypersensitivity reactions occur, the administration of the contrast medium must be discontinued immediately and, if necessary, intravenous treatment initiated.
- the patient should be informed that allergic reactions may develop up to several hours after the procedure; in which case, a physician should be consulted immediately.

In patients taking beta-blockers, hypersensitivity reactions such as drop of blood pressure, bradycardia and bronchospasm may occur more intensely, especially in the presence of bronchial asthma as they may be resistant to treatment with beta-agonists. A higher dose of beta-agonists as the standard dose used for the treatment of hypersensitivity reactions might be required.

Patients with cardiovascular disease are more susceptible to serious even fatal outcomes of severe hypersensitivity reactions.

Hydration

Sufficient hydration should be assured before and after administration of the contrast medium. If necessary, the patient should be hydrated intravenously until excretion of the contrast medium is complete. This applies especially for patients with pre-existing disturbance of renal function, dys- and paraproteinaemia, diabetes mellitus, hyperuricaemia as well as for new-born infants and young children, elderly patients, and patients in poor general condition. In risk patients 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.

Disturbed thyroid function

Following administration of iodinated contrast media, there is a risk either of an exacerbation of hyperthyroidism and thyrotoxic crisis in predisposed patients or induction of hypothyroidism. Patients with manifest but not yet diagnosed hyperthyroidism are at risk as well as patients with latent hyperthyroidism (often patients with nodular goitre) and patients with functional autonomy (often elderly patients, especially in regions with iodine deficiency). In patients who are potentially at risk, thyroid function has to be assessed prior to the examination and hyperthyroidism or autonomy have to be excluded.

Before administering an iodinated contrast agent, make sure that the patient is not about to undergo thyroid scan or thyroid function tests or treatment with radioactive iodine, as administration of iodinated contrast agents, regardless of the route, interferes with hormone assays and iodine uptake by the thyroid gland or metastases from thyroid cancer until urinary iodine excretion returns to normal. Following injection of an iodinated contrast agent, there is also a risk of induction of hypothyroidism. There is as well a risk of hypothyroidism in neonates who have received, or whose mother has received, an iodinated contrast agent.

Cardio-circulatory diseases

Patients with cardio-circulatory diseases are at higher risk for serious changes in cardiac haemodynamics and electrophysiology (pacing and conduction). This is especially applicable following intracoronary, left and right ventricular administration 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 intravasal injection of contrast media can induce pulmonary oedema.

After the investigation: 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.

Impaired renal function

Reversible renal failure or worsening of pre-existent renal failure can occur. Recommended preventive measures are as follows:

- identify at-risk patients. Predisposing factors are: dehydration, a history of renal disease, preceding renal failure following administration of contrast media, existing renal insufficiency, diabetic nephropathy, age over 60 years, children under one year of age, advanced arteriosclerosis, decompensated cardiac insufficiency, high doses of contrast media and multiple injections, direct administration of contrast media to the renal artery, exposition to further nephrotoxins, severe and chronic hypertension, hyperuricaemia and paraproteinaemia (e. g. plasmocytoma, macroglubulinaemia).
- assure sufficient hydration by appropriate water intake prior to and during administration of the contrast medium until renal excretion of the contrast medium is complete.
- avoid concomitant use of nephrotoxic medicines.
- perform repeated examination with a contrast medium only, when the renal function has returned to the base level.

Iodinated contrast media can be administered to dialysis patients as they are eliminated by dialysis.

Impaired liver function

In severe renal insufficiency, an additional severe hepatic impairment can induce serious delayed excretion of the contrast medium, occasionally requiring haemodialysis. 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.

Diabetes mellitus

Prevent lactacidosis in patients with diabetes mellitus treated with metformin (see also section 4.5) Determine serum creatinine levels prior to the intravascular administration of iodinated contrast agents. Depending on the determined kidney function, the interruption of metformin treatment should be considered: Normal serum creatinine: administration of metformin is stopped starting at the time of administration of the contrast medium for 48 hours or until normal renal function is restored. Abnormal renal function: metformin is contraindicated. In an emergency when renal function is unknown: if the investigation is absolutely necessary, precautionary measures must be taken: stop metformin, hydrate, monitor renal function, serum lactate as well as pH and monitor for symptomatology of lactic acidosis.

Coagulopathy

Catheter angiography with contrast media is connected with the risk to induce thromboembolic events. In vitro, non-ionic contrast media have a weaker coagulation inhibiting effect than ionic contrast media. During catheterization it should be considered that besides the contrast medium numerous other factors may also influence the development of thromboembolic events. These are: duration of the examination, number of injections, type of catheter and syringe material, existing underlying diseases und concomitant medication. In order to minimize the examination-related risk for thromboembolism, an especially thorough angiographic method and frequent irrigation of the used catheters shall be observed, and the examination shall be kept as short as possible.

Caution is also advised in patients with homocysteinuria (risk of induction of thromboembolia).

CNS disturbances

The contrast medium should be administered with caution in patients with neurological diseases, as there is an increased risk of neurological complications. Particularly caution is advised in patients with acute cerebral infarction or acute intracranial bleeding as well as in patients with diseases causing disturbance of the blood-brain barrier, in patients with cerebral oedema or acute demyelinisation. Intracranial tumours or

metastases and epilepsy may induce an increased occurrence of seizures following administration of a contrast medium. Neurological symptoms caused by metastases, degenerative or inflammatory processes can be aggravated.

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

Alcoholism/drug dependency

Acute or chronic alcoholism can increase permeability of the blood-brain barrier and thus possibly cause contrast medium-induced CNS reactions.

Further risk factors

Following administration of contrast media to patients with plasmocytoma or paraproteinaemia renal insufficiency may occur. Sufficient hydration is obligatory.

In patients with phaeochromocytoma severe, occasionally uncontrollable hypertensive crisis can develop following intravasal administration of a contrast medium. In patients with phaeochromocytoma pre-treatment with alpha receptor blockers is, therefore, recommended.

The symptoms of myasthenia gravis may be increased by iodinated contrast media.

Among patients with autoimmune diseases cases of serious vasculitis or Stevens-Johnson-like syndromes were observed.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when injected intravenously and intra-arterially. Adequate hydration should be assured.

Precautions and warnings for specific modes of administration

Cerebral arteriography
Serious neurological events have been observed following direct injection of contrast media into cerebral arteries or vessels supplying the spinal cord or in angiocardiography due to inadvertent filling of the carotids. In patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, and previous cerebral thrombosis or embolism and migraine, special caution is advised as cardiovascular reactions such as bradycardia and increases or decreases in blood pressure may occur more often.

Peripheral arteriography
There should be pulsation in the artery into which the contrast medium will be injected. In the presence of obliterative thrombangiitis or ascending infection in combination with severe ischaemia angiography should be performed with special caution, if at all. Vasospasm and subsequent cerebral ischemic phenomena may be caused by intra-arterial injections of contrast media.

Arteriography of the aorta
Depending on the applied technique, injury of the aorta and adjacent organs, pleurocentesis, retroperitoneal bleeding, spinal cord injury and symptoms of paraplegia may occur.

Coronary arteriography and ventriculography
It is absolutely necessary that the examination is performed by specialised staff and that electrocardiograph and sufficient equipment for reanimation and cardioversion are available. During the entire examination, ECG and vital function should be monitored routinely.

During coronary arteriography and left ventriculography, cardiac decompensation, serious arrhythmia, ischaemia and myocardial infarction may occur.

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.

Angiocardiography of right ventricle in paediatric patients
Special precaution should be taken in cyanotic newborns with pulmonary hypertension and cardiac dysfunction.

Supraaortic angiography
Supraaortic angiography should be performed with special attention to the introduction of the catheter. High pressures of the automatic pump can provoke renal infarction, spinal cord lesions, retroperitoneal bleeding, intestinal infarction and necrosis. Renal function should be measured once angiography is concluded.

Phlebography
Special caution should be exercised in patients with suspected thrombosis, phlebitis, serious ischaemia, local infections, or complete venous occlusion. X-ray fluoroscopy is recommended in order to avoid extravasation.

Special populations

Neonates and infants
When examining small children or babies, do not limit fluid intake before administering a contrast medium. Also, correct any existing water and electrolyte imbalance. Especially babies aged less than 1 year and neonates are susceptible to electrolyte disturbances and haemodynamic changes. Caution is, therefore, advised with regard to dosage of the contrast medium, conducting the examination and patient's condition. Premature new-born infants should be monitored very carefully as administration of the contrast medium can result in transient hypothyroidism.

In paediatric patients, one should proceed with great caution when injecting the contrast medium into the right heart chambers of cyanotic neonates with pulmonary hypertension and impaired cardiac function.

In neonates, and particularly in premature neonates, it is recommended that tests of thyroid function (typically TSH and T4), should be checked 7-10 days and 1 month after the administration of iodinated contrast media because of the risk of hypothyroidism due to iodine overload.

Elderly
The elderly are at special risk of reactions due to reduced physiological functions, especially when high dosage of contrast medium is used. Severe vascular and neurological diseases which are present especially in elderly patients, are risk factors for the occurrence of reactions to contrast media. Myocardial ischemia, major arrhythmias and premature ventricular complexes are more likely to occur in these patients. As the renal clearance of iopamidol may be impaired in the elderly, it is particularly important to screen patients aged 65 years and older for renal dysfunction. The probability of acute renal insufficiency is higher in these patients.

Patient preparation
As when using contrast agents there is a possibility of nausea and vomiting fasting should be recommend if considered necessary.

Excipients

<This medicinal product contains […] mmol sodium per dose.>

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with other medicinal products have been performed.

The administration of contrast media may increase the incidence of hypersensitivity reactions in patients taking beta-blockers (see section 4.4). Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists induce decreased efficacy of cardiovascular compensation mechanisms of blood pressure changes.

The administration of X-ray contrast media may induce transient impairment in renal function which may cause lactate acidosis in patients with diabetes mellitus treated with metformin, particularly in patients with impaired renal function. Depending on the results of monitoring of renal function the need for interruption of metformin treatment should be considered (see section 4.4).

In patients being treated with interferons and interleukins, known contrast medium reactions such as erythema, fever and/or flu-like symptoms may occur more frequently and above all delayed.

Medicinal products reducing seizure threshold (e.g. phenothiazine derivates, analeptic agents, tricyclic antidepressants, monoamine oxidase inhibitors, neuroleptic agents) can favour a convulsive seizure especially in patients suffering from epilepsy or focal brain damage. As far as justified by physician's treatment with such medicinal products should be discontinued 48 hours before and up to 24 hours after cerebral angiography in these patients.

Arterial thrombosis has been reported when iopamidol was given following papaverine.

Interactions with diagnostic tests

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

In the diagnosis and treatment of thyroid diseases, Iodine substituted x-ray contrast media can reduce receptivity of the thyroid gland for radio-isotopes for 2 - 6 weeks.

When renal scintigraphy using an injection of radiopharmaceutical secreted by the renal tubule is planned, it should preferably be performed before injection of the contrast agent.

4.6 Fertility, pregnancy and breast-feeding

Pregnancy

There are no adequate data from use of iopamidol in pregnant women.

For reproduction toxicity in animals see section 5.3.

As during pregnancy x-ray exposure should be avoided as far as possible, whether with or without a contrast agent, the benefit of x-ray examination has to be considered carefully.

Apart from radiation exposure of the foetus, benefit-risk-consideration after administration of an iodine-containing contrast agent should also take into account the sensitivity of the foetal thyroid towards iodine, since acute iodine overload following administration of an iodinated contrast agent to the mother can induce foetal thyroid dysfunction.

Breast-feeding

Low amounts of iodinated contrast agents are secreted into the breast milk. Occasional administration to the mother is associated with a low risk of adverse effects for the infant and breastfeeding can be continued.

Fertility

There are no clinical data available with regard to effects on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Ambulant patients while driving vehicles or operating machinery should take into account that nausea may incidentally occur.

4.8 Undesirable effects

Summary of the safety profile

The adverse drug reactions (ADRs) associated with the use of iopamidol are usually of mild to moderate severity and transient. However, severe reactions and in some cases possibly life-threatening reactions can occur that require rapid and effective emergency treatment.
The most commonly reported ADRs are urticaria, nausea, vomiting, pruritus and dyspnoea.

Tabulated list of ADRs

ADRs are reported according to the following frequencies:
<Very common (≥1/10)>
<Common (≥1/100 to <1/10)>
<Uncommon (≥1/1,000 to <1/100)>
<Rare (≥1/10,000 to <1/1,000)>
<Very rare (<1/10,000), not known (cannot be estimated from the available data)>

MedDRA System organ class	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1,000)	**Not known** (cannot be estimated from the available data)
Immune system disorders				Allergoid and/or anaphylactoid reactions: Angioedemas, conjunctivitis, coughing, pruritus, rhinitis, sneezing and urticaria

Endocrine disorders				thyreotoxic crisis
Nervous system disorders			Agitation, confusion, amnesia, speech, sight and hearing disorders, epileptic fits, shaking, paresis, paralyses, paraesthesia, photophobia, transient blindness, coma and somnolence	Transient complications such as dizziness and headache, Thromboembolic events that resulted in a stroke
Cardiac disorders			Clinically relevant disorders of blood pressure, heart rate, cardiac rhythm or cardiac function and cardiac arrest	
Vascular disorders		Thromboembolic events		
Respiratory, thoracic and mediastinal disorders	Transient changes in respiratory rate, shortness of breath and respiratory distress as well as coughing	Bronchospasm, laryngospasm and laryngeal oedema	Pulmonary oedema or respiratory arrest	
Gastrointestinal disorders	Nausea, vomiting, impaired taste	Abdominal complaints	Swelling of salivary glands (iodide mumps)	
Skin and subcutaneous tissue disorders	Oedemas, flush, urticaria, rash, pruritus and erythema		Toxic skin reactions in the form of a mucocutaneous syndrome (e.g. Stevens-Johnson or Lyell's syndrome)	
Renal and urinary Disorders		Renal function disorders		

		extending to acute kidney failure, particularly in patients whose renal function was already impaired		
General disorders and administration site conditions		Feeling warmth, changes in body temperature (fever), headache, feeling unwell, sweating, a cold feeling and vasovagal reactions	Thrombophlebitis and venous thromboses; Inflammation and tissue necrosis	Extravasation local pain and oedemas

Description of selected ADRs

Anaphylaxis (anaphylactoid reactions/hypersensitivity) may manifest with: mild localized or more 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, diffuse erythema, 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. Primary circulatory collapse can occur as the only and/or initial presentation without respiratory symptoms or without other signs or symptoms outlined above. The fall in blood pressure may also be connected with bradycardia (vasovagal reaction), from which tachycardia usually develops over time.

Severe anaphylactic/anaphylactoid reactions in the form of shock are characterised by a massive fall in blood pressure, tachycardia, dyspnoea, agitation, cyanosis, pallor, cold sweats, clouding or loss of consciousness and respiratory and circulatory arrest may result in death. These events can occur rapidly and require full and aggressive cardio-pulmonary resuscitation. Administration of the contrast medium must be discontinued immediately and specific treatment initiated via a venous access (see section 4.4).

After intravascular administration reactions occur, in most cases, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.*

[*For the printed material, please refer to the guidance of the annotated QRD template.]

4.9 Overdose

Dosages exceeding the specific package insert dose are not recommended, as they might lead to life-threatening adverse effects.

An overdose can affect the lungs and the cardiovascular system and thus lead to life-threatening adverse effects. The treatment of overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy. In the event of accidental intravascular overdose in humans, the water and electrolyte losses must be compensated by infusion. Renal function should be monitored for at least three days.

In case of accidental overdose or considerable renal dysfunction, haemodialysis can be used to eliminate Iopamidol from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: x-ray contrast media, iodinated; water-soluble, nephrotropic, low osmolar x-ray contrast media, ATC-Code: V08A B04

X-rays are absorbed by iodine atoms in a stable bound state. The contrast giving effect is based on this absorption.

5.2 Pharmacokinetic properties

Distribution

After intravenous injection, the contrast medium distributes into the intravasal and interstitial space within a few minutes together with a simultaneous renal elimination.

The pharmacokinetics of Iopamidol conform to an open two compartment pharmacokinetic model with first order elimination. Distribution volume is equivalent to extracellular fluid.

Due to its hydrophilic character, there is practically no binding of iopamidol to plasma proteins and cell membranes are not penetrated. It is not possible that iopamidol penetrates the intact blood-brain-barrier.

Biotransformation

There is no evidence of biotransformation.

Elimination

Elimination is rapid. After 120 minutes approx. 50% of the injected contrast medium is excreted with the urine; in case of renal impairment this period of time is prolonged accordingly. Elimination is almost completely through the kidneys. Less than 1 % of the administered dose has been recovered in the faeces up to 72 hours after dosing.

5.3 Preclinical safety data

Intravenous LD_{50}-values in various animal species were determined to be approximately 15-35 fold the maximum clinical dose.

Reproduction Toxicology

There is no evidence for a teratogenic potential of iopamidol. Doses above 1.5 g Iodine/kg/day showed embryotoxic effects in rats and a reduced number of living foetuses and weight of the foetuses. Reduced weight of the foetuses was also observed in rabbits with a dose of 2 g Iodine/kg/day. The fertility of rats as well as the peri- and postnatal development of their offspring was not affected. However, reversible spermatogenesis disorders have been observed in mice after single administration of iopamidol.

Mutagenic Potential

Iopamidol did not show any mutagenic effects in a series of in vitro- and in vivo-tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

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

6.3 Shelf life

[Product specific]

This is a single-dose container. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than […] hours at 2 to 8 °C. Contents not used in a patient during one single investigation as well as contents of a 500 ml vial not used within […] hours during several investigations in one single patient, must be discarded. One container must not be used for several patients.

6.4 Special precautions for storage

<Do not store above 30 °C.>

Keep the <vial><bottle> in the outer carton in order to protect from light. Protect from x-rays.

For storage conditions after first opening please reference to section 6.3.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

[Product specific]

<Not all pack sizes may be marketed.>

6.6 Special precautions for disposal and other handling

Prior to use, the solution has to be inspected visually. Solutions with visible signs of deterioration (such as particles in the solution) must not be used. The vial/bottle should not be used if its integrity is compromised at any time in the preparation of this product.

Any unused portions and waste material derived from disposal and items which come into contact with the product when administering this product with an automatic administration system should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

B. PACKAGE LEAFLET

Package leaflet: Information for the user

{X} 300 mg/ml solution for injection/infusion

Iodine (as Iopamidol)

Read all of this leaflet carefully before you start using 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 radiologist / doctor who will supervise the procedure.
- If you get any side effects, talk to your radiologist / doctor. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet

1. What X is and what it is used for

{X} contains iopamidol, a contrast medium which enhances X-ray contrast. This medicine is for diagnostic use only.

{X} is used in x ray examinations or other imaging techniques (CT-scan). When it is injected into the body, it shows up very well on an X-ray (because iodine blocks X-rays) and is used to help doctors to decide what the problem is.

The following is a list of the most common uses of {X}:
- Examinations of the blood vessels
- Examinations of the heart and its blood vessels
- Computerised tomography (CT) enhancement such as brain or whole body scanning
- Examination of the bladder and urinary tract.

2. What you need to know before X is given to you

You must not be given {X}:
- if you are allergic (hypersensitive) to the active substance iopamidol or any of the other ingredients of {X}.
- if you have overactivity of the thyroid gland (hyperthyroidism)
- if you have a history of major immediate or delayed skin reaction (see section 4.8) to injection of iopamidol

Tell your radiologist/doctor if:
- if you have an overactive thyroid without symptoms (latent hyperthyroidism) and/or thyroid nodule(s) without signs of inflammation (euthyroid goitre)
- if you have kidney or severe liver problems
- if you have (a history of) severe heart or blood vessel (cardiovascular) disease

- if you have bronchial asthma
- if you have diabetes mellitus
- if you have a seizure disorder
- if you have advanced arteriosclerosis (hardening) of arteries supplying the brain
- if you have had an acute stroke
- during acute bleeding in the brain or in conditions accompanied by damage to the blood-brain barrier and swelling of the brain
- if you are in poor overall health or have a fluid deficit (dehydration)
- if you have an abnormality with the proteins or antibodies in your blood such as dysproteinaemia or paraproteinaemia (e.g. in multiple myeloma/plasmocytoma)
- if you have high blood pressure due to a tumour near the kidney (phaeochromocytoma().

Take special care with {X}

1 ml of solution contains … mg of sodium ion at the maximum.

As with all iodine-containing contrast media, dose-independent allergic-like side effects may occur after you have been given Iopamigita. Usually these reactions result in minor symptoms. If such reactions happen, contact your doctor immediately.

Allergic reactions are more common in patients with allergies and/or asthma and also in patients with known allergy to contrast media. If you have a history of allergies or bronchial asthma, you may be given antihistamines and/or corticosteroids before the X-ray investigation.

Iodine-containing contrast media can effect thyroid function. This may induce overactivity of the thyroid gland or even thyreotoxic crisis (over active thyroid gland function in patients with thyroid disease. If you are potentially at risk, then your thyroid function will be assessed prior to the X-ray examination.

Patients with heart and circulation problems, especially those with cardiac weakness, severe coronary heart disease, instable angina pectoris, diseases of the heart valves, previous heart attack, heart bypass and high blood pressure, are at higher risk for serious reactions of the heart. This is especially applicable following intracoronary, left and right ventricular administration of the contrast media.

Patients with diseases of the brain vessels (cerebrovascular diseases), who have had a previous stroke or short term blood vessel constriction or blockage, brain tumour or a wasting or inflammation of the brain are at an increased risk of complications. The presence of brain tumours and epilepsy may lead to an increased risk of seizures. Short or long term alcoholism may cause contrast medium induced reactions of the central nervous system.

The symptoms of myasthenia gravis may be increased by iodinated contrast media.

Among patients with autoimmune diseases cases of serious inflammatory reactions of blood vessels or Stevens-Johnson-like syndromes (life-threatening conditions affecting the skin) were reported.

Catheter X-ray investigations with non ionic contrast media are connected with the risk to sudden blocking of blood vessels or blood clots.

Contrast media may promote changes in red blood cells in individuals with sickle cell disease when injected intravenously and intra-arterially.

Children

Toddlers aged less than 1 year and new-born infants are especially susceptible to an imbalance of salts in the body and haemodynamic changes (blood changes). Caution is, therefore, advised with regard to dosage of the contrast medium, conducting the examination and the patient’s condition.

Other medicines and {X}

Tell your radiologist / doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The administration of X-ray contrast media may induce temporary kidney function impairment which may cause lactate acidosis in patients with diabetes mellitus treated with metformin. Therefore use of metformin must be stopped for a certain period of time before and after the examination.

Especially tell your radiologist / doctor if you take beta blockers (medicines used for high blood pressure, heart problems and other conditions), vasoactive substances (medicines causing constriction or dilation of blood vessels), angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor antagonists (blood pressure lowering medicines). These medicinal products reduce your body's ability to manage changes in blood pressure and hypersensitivity reactions may occur more frequently and, above all, more intensely.

Medicines that reduce the seizure threshold (e.g. phenothiazine derivatives, analeptics, tricyclic antidepressants, monoamine oxidase inhibitors, antipsychotics) may facilitate seizures especially in patients with epilepsy or focal brain damage. If medically acceptable, treatment with such medicines should be suspended for 48 hours before and up to 24 hours after cerebral angiography in such patients.

In patients who have been treated with interferons and interleukins, known contrast medium reactions such as skin redness, fever and/or flu-like symptoms may occur more frequently and, above all, with a time lag.

Arterial thrombosis has been reported when iopamidol was given following papaverine.

The administration of vasopressors strongly potentiates the neurological effect of the intra-arterial contrast media.

Diagnostic tests and {X}

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

Iodine containing x-ray contrast media can reduce the ability of the thyroid gland to take up radio-isotopes used in the diagnosis and treatment of thyroid disease for 2-6 weeks.

When renal scintigraphy using an injection of radiopharmaceutical secreted by the renal tubule is planned, it should preferably be performed before injection of the contrast agent.

{X} with food and drink

There are no known interactions between {X} and food and drinks. However, please check with your doctor, radiologist if it is required not to eat anything for 2 hours prior to the investigation. You should drink, however, sufficient amounts of water before the examination.

Pregnancy

You must tell your doctor if you think you are or might become pregnant. Safe use of iopamidol in pregnant women has not been established. When a pregnant woman has an x-ray examination, the child in her womb will also be exposed to radiation. For this reason alone, the benefit of any x-ray examination, with or without a contrast medium, must be carefully considered. Apart from trying to avoid foetal radiation exposure wherever possible, the benefit-risk assessment of the use of iodine containing contrast media should also take account of the iodine sensitivity of the foetal thyroid gland.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. Low amounts of iodinated contrast agents are secreted into the breast milk. Occasional administration to the mother is associated with a low risk of adverse effects for the infant. As a precautionary measure, breast-feeding should be discontinued for at least 24 hours after you receive {X}.

Driving and using machines
Your injection is unlikely to affect your ability to drive a car or to operate machines. However, while driving vehicles or operating machines you should take account that nausea or low blood-pressure may incidentally occur.

3. How X will be given to you

{X} will be given by an authorised healthcare professional directly into a vein or an artery.

Ideally you should be recumbent during administration, and you will be kept under supervision for at least 30 minutes after the injection by your radiologist/doctor. This is the time where most undesired reactions (e. g. allergic reactions) may occur. However, in rare cases, reactions may occur after hours or days.

If this medicinal product is intended to be used with an automatic administration system, its suitability for the intended use has to be demonstrated by the manufacturer of the medical device. Instructions for use of the medical device must be followed absolutely.

This medicinal product is for single use only. Multiple injections or repeated examinations are possible.

Adults, adolescents and children
Unless prescribed otherwise by your doctor, the dose will depend on the type of examination to be performed on you, your age, weight, heart function and general state of health, and the type of examination that is being used. The dose recommendations at the end of this leaflet are based on general experience with non-ionic x-ray contrast media as well as clinical studies performed with iopamidol. The total volume administered should not exceed 250 ml.

Unless indicated otherwise, the dosage for children depends on their age and body weight, and should be determined by the attending physician.

Dosage in special patient groups

Patients with impaired renal function
The dosage of contrast media will be kept as low as possible.

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

Elderly
No dosage adjustment is considered necessary.

If you are given more {X} than you should
This medicine will be given to you by a healthcare professional. If you think that you have received too much medicine please tell your doctor or nurse immediately. In case of accidental overdose or significantly impaired kidney function, iopamidol can be removed from the body by dialysis.
If you have any further questions on the use of this product, ask your radiologist / doctor.

4. Possible side effects

Like all medicines, {X} can cause side effects, although not everybody gets them. Side effects you may get after being given a contrast medium like {X} are usually mild to moderate and do not last long.

The most commonly reported side effects with {X} are urticaria, nausea, vomiting, pruritus and dyspnoea.

Other side effects that may occur have been listed by frequency:

Frequency	**Adverse reaction**
Common (affects 10 to 100 users in 1,000)	- Temporary changes in breathing rate; shortness of breath; difficulty breathing as well as coughing - Nausea; vomiting; problems with your sense of taste - Swelling of the hands, ankles or feet (oedemas); flush; nettle rash; rash; itching; redness of skin
Rare (affects 1 to 10 users in 10,000)	- X-ray procedures of the brain and other procedures in which the contrast media enters the arterial blood in the brain in a high concentration: agitation; confusion; loss of memory; speech, sight and hearing disorders; epileptic fits; shaking; weakness causing loss of movement; paralyses; tingling or numbness of the hands or feet (pins and needles); increased sensitivity to light; temporary blindness; coma; drowsiness - Blockage of a blood vessel by a blood clot have been reported during catheter angiographic examinations, which resulted in heart attack - Difficulty in breathing or wheezing, swelling or spasm of the voice box (larynx). - Stomach complaints - Kidney function disorders extending to acute kidney failure, particularly in patients whose renal function was already impaired - Serious life-threatening reactions (including fatalities) that require emergency treatment and are associated with vital functions of the cardiovascular system, usually in connection with respiratory and central nervous reactions: Feeling warmth; changes in body temperature (fever); headache; feeling unwell; sweating; a cold feeling; fainting
Very rare (affects less than 1 user in 10,000)	- Clinically relevant disorders of: blood pressure; heart rate; fast, slow or irregular heartbeats; pain or tightness in the chest; heart failure; heart attack - Swelling or fluid in the lungs; stopped breathing (respiratory arrest) - Swelling of salivary glands in and around the mouth (iodide mumps) - Swelling of the face, skin, tongue, other mucous membranes (e.g. inside nose or mouth) or other parts of the body; severe skin disease (red, blistered, bleeding, painful skin, which may affect the lips, eyes, mouth, nose and genitals too). - Swelling and redness along a vain which is extremely tender when touched; blood clots of the veins - Injection site reactions: inflammation and soft tissue infections
Not known (frequency cannot be estimated from the available data)	- Altered thyroid gland function or a severe form of overactive thyroid (thyrotoxic crisis) - Blockage of a blood vessel by a blood clot that results in a stroke - Temporary complications such as dizziness and headache - Injection site reactions: if the injection does not go directly into the blood vessel; local pain and swelling (oedemas)

Some people may find they have an allergic reaction to {X}. **Tell your radiologist or X-ray staff immediately** if any of the following rare severe allergy symptoms occur:

- Itchy or watery eyes, coughing, runny or blocked nose, sneezing;
- Swelling of eyelids, face, lips or throat
- Skin rashes, itchiness, fever
- Sudden wheeziness and tightness of the chest, difficulty in breathing, feeling of suffocation
- Agitation, blue lips, blue or pale skin, cold sweats
- Headache, dizziness, feeling faint, clouding or loss of consciousness, collapse (a massive fall in blood pressure, increased heart rate)

Reporting of side effects

If you get any side effects, talk to your doctor or radiologist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.* By reporting side effects you can help provide more information on the safety of this medicine.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

5. How to store X

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

This medicine should not be used after the expiry date that is stated on the label<carton> <bottle> <…> <after {abbreviation used for expiry date}.>. The expiry date refers to the last day of that month.

Keep the <vial><bottle> in the outer carton in order to protect from light.

<Do not store above 30 °C.>

Chemical and physical in-use stability has been demonstrated [..] hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.

This medicine should not be used if any visible signs of deterioration (such as particles in the solution or fissures in the vial) are noticed.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What X contains

- The active substance is iopamidol.
  1 ml solution for injection contains 612.4 mg iopamidol, equivalent to 300 mg iodine..
- The other ingredients are [product specific]

What X looks like and contents of the pack

Solution for injection.

Clear colourless or light yellow solution.

[Nature and contents of the container - product specific]

{X} is presented in the following packs:

[Product specific]

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

<---------->

The following information is intended for medical or healthcare professionals only:

Dose recommendations

Intravenous or intra-arterial use (injection or infusion).

Intraarterial administration

	Adults	Children
Cerebral Arteriography (non-selective)	Sheet film angiography: 40-60 ml Digital subtraction angiography: 20 – 30 ml.	The dosage depends on the body weight and age.
Cerebral Arteriography (selective)	Sheet film angiography: 4-12 ml Digital subtraction angiography: 3 – 8 ml	
A. pulmonalis	Digital subtraction angiography 25 ml per single injection; overall dose up to 170 ml	
Other regions	Sheet film angiography: The volume of the single injection depends on the vascular region to be examined. Maximum of 250 ml. Digital subtraction angiography: 30 – 50 ml. The volume of the single injection depends on the vascular region to be examined. Maximum of 250 ml.	
Angiocardiography	The volume of the single injection depends on the vascular region to be examined. Maximum of 250 ml.	The dosage depends on the body weight and age.

Coronary angiography	4 - 10 ml/artery, to be repeated if required	

Intravenous administration

	Adults	Children
Phlebography	50 ml, depending on body weight and age	
Intravenous digital subtraction angiography (i.v. DSA)	30 - 50 ml, to be repeated if required	The dosage depends on the body weight and age.
Computer tomography (CT)	1 – 2 ml/kg body weight	The dosage depends on the body weight and age.
Excretory urography	50-100 ml	0 – 1 month 4 - 5-(6) ml/kg 1 – 3 month 4 ml/kg 3 – 6 month 3.5 - 4 ml/kg 6 – 12 month 3 – 3.5 ml/kg 12 – 24 month 2.5 - 3 ml/kg 2 – 5 years 2.5 ml/kg 5 – 7 years 2 – 2.5 ml/kg 7 – 12 years 1.5 – 2 ml/kg

The maximum dose for iopamidol with 300 mg Iodine/ml is 2 ml/kg bodyweight.

Dosage adjustments in specific patient groups is required such as in patients with renal impairment and hepatic impairment.

Administration

The contrast medium should be brought to body temperature before administration. Experience has shown that a warmed contrast medium is tolerated better.

Contrast media should normally not be drawn up into a syringe until immediately before use. To minimise the risk of thromboembolism associated with the examination, the contact time between blood and contrast medium in syringes and catheters should be kept as short as possible. Attention should also be paid to careful angiographic technique and frequent flushing of catheters with sodium chloride 9 mg/ml (0,9%) solution for injection (adding heparin if necessary). Contrast medium not completely used up during an examination must be discarded.

The contrast medium should be administered to the recumbent patient if at all possible. Immediate repositioning must be possible. To enable emergency management if necessary, a secured venous access should be in place before starting the examination. Like all iodine containing x-ray contrast media, Iopamigita should be used with any diagnostic technique only if resuscitative equipment and emergency medication are available.

In patients with impaired renal function, cardio-circulatory insufficiency as well as bad general condition, the dosage of contrast media should be kept as low as possible. Kidney function should be monitored at least three days following the examination.

Precautions for use

Pretesting using a low dose of contrast medium for hypersensitivity is not recommended, as this not meaningful and occasionally resulted in serious hypersensitivity reactions.

Iodine-containing contrast media should only be used under the precondition that treatment of emergencies is possible. This includes availability of the necessary technical and medicinal equipment. Following administration, the patient shall be monitored for at least ½ hour, as from experience the majority of all serious incidents occur within this timeframe. All medical and nursing staff must be informed of adverse reactions as well as general and pharmacological emergency measures.

The patient must be kept sufficiently hydrated before and after the examination. Any fluid and electrolyte imbalance should be corrected. In patients with dysproteinaemia or paraproteinaemia (multiple myeloma/plasmacytoma), diabetes mellitus, polyuria or oliguria, gout, as well as in young children, old patients and patients in poor general condition, fluid intake must never be restricted before administering the contrast medium. In patients at risk, the water and electrolyte balance should be monitored, watching for symptoms of decreasing serum calcium levels.

Reversible kidney failure can occur in rare cases. A history of or existing kidney disease, age over 60 years, fluid imbalance, advanced arteriosclerosis, decompensated heart insufficiency, high doses of contrast media and multiple injections, direct administration of contrast media to the renal artery, exposition to further medicines which may damage the kidneys, severe and chronic high blood pressure, hyperuricaemia and paraproteinaemia (e. g. plasmocytoma, macroglubulinaemia) are predisposing factors.

In patients with impaired kidney function, the use of potentially kidney damaging medicines should, if at all possible, be avoided until excretion of the contrast medium is complete. Further contrast medium examinations should be postponed until kidney function has returned to baseline.

Iodine-containing contrast media can be removed from the blood by dialysis.

As the intravascular administration of iopamidol can lead to renal failure, metformin must be discontinued prior to, or at the time of the test and not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Please refer to the SmPC for further information.

What to do in the event of side effects?

If an adverse reaction occurs, administration of the contrast medium must be stopped immediately. Treatment should be in response to the clinical picture e.g. general treatment (antihistaminic, corticosteroids, oxygenotherapy),treatment of cardiovascular disorders (vasopressors, plasma, electrolytes), treatment of convulsions (diazepam), treatment of tetanic crisis (calcic gluconate), Renal function should be monitored at least the following 3 days after overdose. General resuscitative measures and the use of medicines may be necessary. It should be borne in mind that the effects of adrenaline and volume replacement are reduced in patients co-administered β-receptor blockers.

Shelf-life after first opening

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than [...] hours at 2 to 8 °C.