Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Niopam 370, Solution for Injection, glass bottles

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The solution contains 75.53% w/v Iopamidol, equivalent to 370 mg Iodine/ml.

Each ml contains 755.3mg Iopamidol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.
A clear aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

X-ray contrast medium for use in angiography, left ventriculography and coronary arteriography and urography.

4.2 Posology and method of administration

Method of administration
Intraventricular
Intra-arterial
Intravenous.

Posology

NIOPAM 370 : DOSAGE SCHEDULE

Procedure	Dosage
Peripheral arteriography	Adults 10 - 50ml* Children * *
Venography	Adults 20 - 50ml Children * *
Angiocardiography and left ventriculography	Adults 30 - 80ml Children * *
Coronary arteriography	Adults 4 - 8ml per artery
Aortography - retrograde	Adults 30 - 80ml Children * *
Selective renal arteriography	

Hepatic Coeliac Superior Mesenteric Inferior Mesenteric	Adults 30 - 70ml 40 - 70ml 25 - 70ml 5 - 30ml Children * *
Selective visceral angiography Intravenous Injection Left ventriculography Selective Coronary Arteriography by Intra-Arterial DSA	 Adults 30 - 70ml Children 40 - 70ml Adults 25 - 70ml Children 5 - 30ml Adults 2 - 5ml
Intravenous Urography	Adults 40 - 80ml In severe renal failure the usual high dose methods should be employed (up to 1.5ml/kg) Children 1 - 2.5ml/kg or * *

* Repeat as necessary
* * According to body size and age

Elderly: Dosage as for adults.

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.

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 iopamidol solution for injection.

4.3 Contraindications

Hypersensitivity to the active ingredient iopamidol or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

During the examination an intravenous route for emergency treatment in the event of a reaction is required.
After the administration of the contrast medium, competent personnel, drugs and equipment for emergency resuscitation must be available for at least 30 minutes**.**

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

media.

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

Iopamidol injection should be used with caution in patients with hypercalcaemia and cerebral vascular disease.

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

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

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

In patients with suspected or known hypersensitivity to contrast media, sensitivity testing is not recommended, as severe or fatal reactions to contrast media are not predictable from sensitivity tests.
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.

The risk of bronchospasm-inducing reactions in asthmatic patients is higher after contrast media administration.

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. All other patients should be observed for at least 30 minutes after the procedure as most of the adverse events occur within this period.

In patients undergoing angiocardiographic procedures special attention should be paid to the status of the right heart and pulmonary circulation.Special care should be exercised when this product is injected into the right heart or pulmonary artery in patients with pulmonary hypertension. 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.

Particular care should also be exercised in patients with moderate to severe impairment of renal function (as reflected by a raised blood urea) or in diabetes. Pre-existing renal impairment may predispose to acute renal dysfunction following contrast media administration. In patients with impairment of renal function, the administration of potentially nephrotoxic drugs should be avoided until the contrast medium is completely excreted. In such patients, renal function parameters should be monitored after the procedure. Further administration of contrast media should be postponed until renal function has returned to its previous level.

Care should be taken in renal impairment and diabetes. In these patients it is important to maintain hydration in order to minimise deterioration in renal function.

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

Hydration
Patients must be well hydrated, and any relevant abnormalities of fluid or electrolyte balance should be corrected prior to and following contrast media injection. Especially patients with severe functional impairment of the kidneys, the liver or myocardium, myelomatosis, or other paraproteinaemias, sickle cell disease, diabetes mellitus, polyuria, oligouria, hyperuricaemia, infants, elderly patients, and patients with severe systemic disease should not be exposed to dehydration. Caution should be exercised in hydrating patients with underlying conditions that may be worsened by fluid overload, including congestive heart failure.

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.

Niopam should be used with caution in patients with hyperthyroidism. 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.

Phaeochromocytoma
Patients with phaeochromocytoma can develop severe hypertensive crises following intra-arterial and β iopamidol administration. Premedication with a-receptor blockers is recommended before intra-arterial injection of contrast media under the supervision of a physician.

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.

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.

In patients undergoing peripheral angiography, there should be pulsation in the artery into which the X-ray contrast medium will be injected. In patients with thromboangiitis obliterans or ascending infections in combination with serious ischaemia the angiography should be performed, if at all, with special caution.

Iopamidol should be administered with caution in patients withCNS disordersand altered permeability of the blood-brain barrier, such as increased intracranial pressure, suspicion of intracranial tumor, abscess or hematoma/hemorrhage, history of convulsive disorder, alcoholism.
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 Niopam (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 Niopam should be withheld. If the patient has developed a severe cutaneous adverse reaction with the use of Niopam, Niopam must not be re-administered in this patient at any time.

Use in Special Populations
Newborns, children
Infants (age<1year), and especially newborns are particularly susceptible to electrolyte imbalances and haemodynamic alterations.
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.

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.

Women of child-bearing potential

X-ray examination of women should if possible be conducted during the pre-ovulation phase of the menstrual cycle and should be avoided during pregnancy; also since it has not been demonstrated that Niopam is safe for use in pregnant women, it should be administered only if the procedure is considered essential by the physician.
Iopamiro contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per bottle, that is essentially "sodium-free".

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 (Metformin), these agents should be stopped prior to an intraarterial contrast medium administration with first pass renal exposure, or in patients with acute kidney injury, and re-instated only after 48 hours if renal function hasn´t changed significantly. (See 4.4 Special warnings and precautions for use: Special populations)..

Beta-blockers may impair the management of bronchospasm and the response to adrenaline.

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. Therefore, administration of intravascular contrast agents should be postponed in patients who have recently been given a cholecystographic contrast agent.
Contrast media may interfere with laboratory tests for bililrubin, 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.

Following administration of iopamidol, the capacity of the thyroid tissue to take up iodine is reduced for 2-6 weeks.
Use of the product may interfere with tests for thyroid function.

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

4.6 Fertility, pregnancy and lactation

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).
Iodine-containing X-ray contrast agents are excreted into the breast milk in low amounts. From animal experience, Niopam is non toxic in animals after oral administration. From experience gained so far, harm to the nursing infant is unlikely to occur.Stopping breastfeeding is unnecessary.

4.7 Effects on ability to drive and use machines

There is no known effect on the ability to drive and operate machines.

4.8 Undesirable 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 Niopam 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.

4.8.1. Intravascular administration

Adult subjects

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
Immune system disorders				Anaphylaxis, Anaphylactoid reaction
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, Hemiplegia, Contrast induced encephalopathy**
Eye disorders				Blindness transient, Visual disturbance, Conjunctivitis, Photophobia
Cardiac disorders		Cardiac dysrhythmias such as extrasystoles, atrial fibrillation, ventricular tachycardia and ventricular fibrillation*	Bradycardia	Myocardial ischaemia or infarction, Cardiac failure, Cardi, o-respiratory arrest, Tachycardia, Kounis syndrome
Vascular disorders		Hypotension, Hypertension, Flushing		Circulatory collapse or shock
Respiratory, thoracic and			Pulmonary oedema,	Respiratory arrest, Respiratory failure, Acute respiratory distress syndrome,

mediastinal disorders			Asthma, Bronchospasm	Respiratory distress, Apnoea, Laryngeal oedema, Dyspnoea
Gastrointestinal disorders	Nausea	Vomiting, Diarrhea, Abdominal pain, Dry mouth		Salivary hypersecretion, Salivary gland enlargement
Skin and subcutaneous tissue disorders		Rash, Urticaria, Pruritus, Erythema, Sweating increased		Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme Skin necrosis***, Face oedema, Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		Back pain	Muscle spasms	Compartment syndrome***, Musculoskeletal pain, Muscular weakness
Renal and urinary disorders		Acute renal failure		
General disorders and administration site conditions	Feeling hot	Chest pain, Injection site pain, Pyrexia, Feeling cold	Injection site swelling	Rigors, Pain, Malaise Injection site inflammation**,
Investigations		Blood creatinine increased		Electrocardiogram change including ST segment depression

* Cardiac dysrhythmias may occur mostly after cardiac angiographic and coronary catheterization procedures
**Contrast induced encephalopathymay manifest with symptoms and signs described in section 4.4
*** On very rare occasions extravasation of contrast medium led to inflammation (manifested with local erythema, oedema and blisters), skin necrosis and compartment syndrome
Coronary artery thrombosis has been reported as a complication of coronary catheterization procedures.
Other cardiac reactions which may occur as a consequence of the procedural hazard include coronary artery dissection.

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. 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 vasodilatation with pronounced hypotension, tachycardia, dyspnoea, agitation, cyanosis and loss of consciousness progressing to respiratory and/or cardiac arrest may result in death. These events can occur rapidly and require full and aggressive cardio-pulmonary resuscitation.
Primary circulatory collapse can occur as the only and/or initial presentation without respiratory symptoms or without other signs or symptoms outlined above.

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.

4.8.2. 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.
Blood amylase increased is common following ERCP. 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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

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

If needed, hemodialysis 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
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Iopamidol is contrast medium belonging to the new generation of non-ionic compound whose solubility is due to the presence of hydrophilic substitutes in the molecule. This results in a solution of low osmolality when compared with ionic media.

5.2 Pharmacokinetic properties

The pharmacokinetics of iopamidol conforms to an open two compartment pharmacokinetic model with first order elimination.

Distribution volume is equivalent to extracellular fluid.

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. Elimination is rapid; up to half the administered dose may be recovered in the urine in the first two hours of dosing.

There is no evidence of biotransformation.

Serum protein binding is negligible.

5.3 Preclinical safety data

No adverse effects can be predicted from animal toxicology studies other than those documented form human use of iopamidol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium Calcium Edetate
Hydrochloric acid (for pH adjustment)

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

5 years.
In use shelf life: Once opened, use immediately.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Colourless Ph. Eur. Type I or Type II glass bottle with rubber closure and aluminium cap.
Quantities of 30, 50, 70, 100, 200, 250, or 500 ml of solution.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Discard if the solution is not clear of particulate matter.

Exceptionally, the event of crystallisation of Niopam could occur. It has been shown that such a phenomenon is caused by a damaged or defective container and therefore the product should not be used in this case.

The bottle, once opened, must be used immediately. Any residue of contrast medium must be discarded.

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

Niopam, 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

Bracco Imaging spa
via Egidio Folli 50
20134 Milan
Italy

8 MARKETING AUTHORISATION NUMBER

PA1826/004/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10March 1983

Date of last renewal: 08 March 2008

10 DATE OF REVISION OF THE TEXT

January 2023