16 OTT 2023
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GRAFICA - FOTOCOMPOSIZIONE
Via G. Tartini, 2 - 20158 - MILANO
AZIENDA CERTIFICATA UNI EN ISO 9001:2015

FCI003L05-PIL-IOPA
Versione interna: 01

Impianto di proprietà della:	BRACCO	*Bracco s.p.a. via E. Folli, 50 - 20134 Milano - Italy*
patheon by Thermo Fisher Scientific	*Patheon Italia S.p.A. viale G.B. Stucchi, 110 - 20900 Monza (MB) - Italy*	*Cliente:* **BRACCO s.p.a.**

Prodotto: **IOPAMIRO (INDONESIA)**

SPECIFICA RIFERIMENTO: **SF0003 IS+P**	*Materiale:* **Istruzione**	*Codice Patheon:* **000000**	*Codice Patheon superato:* **251810**	*Codice Bracco:* **CI003L05**	*Codice Bracco superato:* **CI003L04**

Dimensioni: **150x560 mm**	Stesa ☒	Piegata ☒	Bobina ☐	Pre taglio ☐	CODICE LAETUS	*Apri nota digitale se presente*

Colori n°:	Black					
01						

Modifica rispetto la versione precedente: **SAFETY UPDATE OF PACKAGE INSERT FOR POST MARKETING AES**

Packaging Development	*Data Emissione*	*Data Obsolescenza*	*Status*

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Iopamiro®

Iopamidol

BRACCO

The product Iopamiro (Iopamidol) was discovered and developed in the research laboratories of Bracco (Milan - Italy). Chemically the substance is: (S)-N,N'-bis [2-hydroxy-1-(hydroxymethyl)-ethyl]-2,4,6-triiodo-5-lactamido-isophthalamide.

Iopamiro is a x-ray contrast medium of the new generation of non ionic compounds, which are water soluble because the molecular structure incorporates hydrophilic groups. This new class of contrast media differs significantly from other compounds currently used in connection with radiological procedures, all of which are soluble only when the radiopaque molecule is ionised by forming a salt with sodium and/or meglumine.

While such products are remarkably well tolerated, their aqueous solutions show an inherently high osmolality and this is responsible for a number of side effects that may occur after administration. The discovery of non ionic contrast agents has afforded, along with a sizable reduction of general toxicity, a considerable improvement in local and tissue tolerability, even by the more delicate structures of the human body such as vascular endothelia and the central nervous system. The product is available as preconstituted solution in different concentrations, with the following physical properties:

Concentration		*Viscosity mPa.s*		*Relative density* d^{20}_{4}	*Osmometric values at 37°C*		*pH*
mg iodine/ml	*g iopamidol/100ml*	*20°C*	*37°C*	*20°C*	*Osmolality (osmol.kg-1)*	*Osmotic pressure (atm)*	
300	61.2	8.8	4.7	1.33	0.616	15.7	7 ± 0.5
370	75.5	20.9	9.4	1.41	0.796	20.3	7 ± 0.5

The low osmotic pressure of solutions, the nonionic nature of the molecule and its inherently low chemotoxicity contribute to the exceptionally good local and systemic tolerability of Iopamiro. The favourable results of extended biological and clinical investigations confirm the suitability of Iopamiro as a contrast medium for intrathecal, intra-arterial and intravenous administration.

INDICATIONS

NEURORADIOLOGY: myeloradiculography, cisternography and ventriculography.
ANGIOGRAPHY: cerebral arteriography, coronary arteriography, thoracic aortography, abdominal aortography, angiocardiography, selective visceral arteriography, peripheral arteriography, venography, digital subtraction angiography (DSA), DSA of cerebral arteries, DSA of peripheral arteries, DSA of abdominal arteries.
UROGRAPHY: intravenous urography.
CONTRAST ENHANCEMENT IN CT SCANNING. ARTHROGRAPHY. FISTULOGRAPHY.

CONTRAINDICATIONS

There are no definite or absolute contraindications to the use of Iopamiro, with the possible exception of Waldenström's macroglobulinemia, multiple myeloma, and severe liver and kidney diseases.

GENERAL WARNINGS AND SIDE EFFECTS

The use of organic iodine compounds may cause untoward side effects and manifestations of anaphylaxis.

The symptoms include nausea, vomiting, widespread erythema, generalized heat sensation, headache, coryza or laryngeal edema, fever, sweating, asthenia, dizziness, pallor, dyspnoea and moderate hypotension. Skin reactions may occur in the form of various types of rash or diffuse blister formation.

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 Iopamiro. 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. More severe reactions involving the cardiovascular system such as peripheral vasodilation with pronounced hypotension, tachycardia, dyspnoea, agitation, cyanosis and loss of consciousness, may require emergency treatment. For these reasons the use of organic iodine contrast media must be limited to cases for which the diagnostic procedure is definitely indicated, as suggested by the patient's clinical status with special attention to existing pathology of the cardiovascular, urinary or hepatobiliary system. In particular, contrast media designed for cardioangiographic 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 iodinized contrast media, the public or private institutions, where such procedures take place, should be supplied at all times with all equipment and drugs that experience has shown to be suitable in case of an accident: the Ambu balloon, oxygen bottles, antihistamines, vasopressor drugs, cortisones.

Never mix other drugs with contrast medium solutions. When examining small children or babies, do not limit fluid intake before administering a hypertonic contrast solution; also, correct any existing water and electrolyte imbalance. Pregnant women and patients with hyperthyroidism should receive iodinized contrast media only if the attending physician finds it absolutely necessary. In patients scheduled for thyroid examination with a radioactive iodine tracer, bear in mind that iodine uptake in the thyroid gland will be reduced for several days (sometimes up to 2 weeks) after dosing with an iodinized contrast medium that is eliminated through the kidneys.

Encephalopathy has been reported with the use of Iopamidol. 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.

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.

<u>During post-marketing surveillance,</u> the following adverse events have been reported after intravascular administration of Iopamiro:
Blood and lymphatic system disorders: thrombocytopenia.
Immune system disorders: anaphylaxis, anaphylactoid reaction.
Nervous system disorders: 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: myocardial ischaemia or infarction, cardiac failure, cardio-respiratory arrest, tachycardia, Kounis syndrome.
Vascular disorders: circulatory collapse or shock.
Respiratory, thoracic and mediastinal disorders: respiratory arrest, respiratory failure, acute respiratory distress syndrome, respiratory distress, apnoea, laryngeal oedema, dyspnoea.
Gastrointestinal disorders: salivary hypersecretion, salivary gland enlargement.
Skin and subcutaneous tissue disorders: face oedema, acute generalised exanthematous pustulosis (AGEP), erythema multiforme.
Musculoskeletal and connective tissue disorders: musculoskeletal pain, muscular weakness, compartment syndrome.
General disorders and administration site conditions: rigors, pain, malaise, injection site inflammation.
Investigations: electrocardiogram change including ST segment depression.

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

NEURORADIOLOGY

	Concentration (mg iodine/ml)	*Recommended dosage (ml)*
Myeloradiculography	300	5-15
Cisternography and ventriculography	300	5-15

Warnings and side effects

In the event of CSF blockade, remove as much of the administered contrast solution as possible. The use of organic iodine contrast media may be contraindicated for patients with a history of epilepsy. Also the presence of blood in the CSF contraindicates the use of Iopamiro: in such cases, the operator should carefully assess the need for the diagnostic procedure against possible risk to the patient. 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.

Neuroleptics must be absolutely avoided because they lower the seizure threshold. The same applies to analgesics, antiemetics, antihistamines and sedatives of the phenothiazine group. Whenever possible, treatment with such drugs should be discontinued at least 48 hours before administration of the contrast medium and not be resumed less than 12 hours after completion of the procedure.

SENSO MACCHINA LETTURA CODICE

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Clinical trials have shown that Iopamiro is readily tolerated by the vast majority of patients, both in general terms and, particularly, in terms of CNS tolerability. Reported side effects include headache (sometimes with a delayed onset), nausea, vomiting and pain at the site of injection, all these manifestations being generally mild and of short duration. More rarely or indeed exceptionally, patients have developed dizziness, neck rigidity, lumbar pain, or sciatic pain - the latter often as a transient exacerbation of pre-existing symptoms. Fever was reported in a few cases. Exceptionally, patients dosed with Iopamiro have developed muscular spasms or generalized convulsions, sometimes representing a recurrence of established epilepsy or attributable to accidental overdosage of neuroleptic drugs. Very few cases of transient mental confusion have been reported.

During post-marketing surveillance, the following adverse events have been reported after intrathecal administration:
Infections and infestations: meningitis aseptic, meningitis bacterial as consequence of the procedural hazard.
Immune system disorders: anaphylaxis, anaphylactoid reaction.
Psychiatric disorders: confusional state, disorientation, agitation, restlessness.
Nervous system disorders: coma, paralysis, convulsion, syncope, depressed level of consciousness or loss of consciousness, meningism, dizziness, paraesthesia, hypoaesthesia, contrast induced encephalopathy.
Eye disorders: blindness transient.
Cardiac disorders: arrhythmia.
Vascular disorders: hypertension.
Respiratory, thoracic and mediastinal disorders: respiratory arrest, dyspnoea
General disorders and administration site conditions: pyrexia, malaise, rigors.

ANGIOGRAPHY

	Concentration (mg iodine/ml)	Recommended dosage (ml)
Cerebral arteriography	300	5-10 (bolus)
Coronary arteriography	370	8-15 (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	depending on examination
Peripheral arteriography	300-370	40-50
Digital subtraction angiography	370	depending on examination
Venography	300	30-50

Warnings and side effects
The use of Iopamiro as a contrast medium for cerebral angiography, may cause side effects, which are usually mild and of short duration. Many patients report a sensation of heat in the face and neck; a few complain of headache. A fairly frequent cardiovascular reaction to dosing with Iopamiro is bradycardia associated with systemic hypotension. The reaction is transient and requires no treatment. Severe neurological sequelae may arise as direct complications of pre-existing pathology in the individual patient. Such reactions are diverse and may include tonic/clonic convulsions, aphasia, fainting, transient narrowing of visual field, hemiparesis and coma. The risk associated with a particular investigation involved may be increased by conditions such as advanced arteriosclerosis, hypertension, heart failure, major systemic diseases and recent cerebral embolism or 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. In paediatric roentgenology, 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 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. Likewise, in abdominal aortography, excess pressure from the pump may cause renal infarction, spinal cord injury, retroperitoneal bleeding, intestinal infarction and necrosis. In peripheral arteriography Iopamiro 370 may sometimes cause a painful reaction in the involved limb.
This is usually not the case with the less concentrated solution Iopamiro 300.

A property of nonionic contrast media is the extremely low interference with normal physiological functions. As a consequence of this, nonionic contrast media have less anticoagulant activity in vitro than ionic media. Medical personnel performing vascular catheterisation procedures should be aware of this and pay meticulous attention to the angiographic technique and catheter flushing so as to minimize the risk of procedure-related thrombosis and embolism.

The side effects reported in post-marketing surveillance, in connection with angiography, are those described in the paragraph on general warnings and side effects.

UROGRAPHY
Iopamiro 300 and 370 should be used; the dose recommended for this type of examination is 30 to 50 ml.
The less marked osmotic diuresis induced by the nonionic 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.

Warnings and side effects
The side effects that may arise in connection with intravenous urography are those described in the paragraph on general warnings and side effects.

OTHER DIAGNOSTIC PROCEDURES

	Concentration (mg iodine/ml)	Recommended dosage (ml)
Contrast enhancement in CT scanning	300-370	0.5 - 2.0/kg
Arthrography	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.

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

The side effects reported in post-marketing surveillance, in connection with CT scanning, are those described in the paragraph on general warnings and side effects.

STORAGE CONDITION
Store below 30°C and in dry place.
Keep Iopamiro solutions away from strong light. Exceptionally, the event of crystallization of Iopamiro solutions 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. 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.

COMPOSITION & REGISTRATION NUMBER
Iopamiro 300 - Each vial (50 ml) contains: 30.62 g of Iopamidol Reg No : DKI2110400343A1
Iopamiro 300 - Each bottle (100 ml) contains: 61.24 g of Iopamidol Reg No : DKI2110400343A2
Iopamiro 370 - Each vial (50 ml) contains: 37.76 g of Iopamidol Reg No : DKI2110400343B1
Iopamiro 370 - Each bottle (100 ml) contains: 75.53 g of Iopamidol Reg No : DKI2110400343B2

HOW SUPPLIED
Iopamiro 300 - Boxes of 1 bottle, 50 ml - Boxes of 1 bottle, 100 ml
Iopamiro 370 - Boxes of 1 bottle, 50 ml - Boxes of 1 bottle, 100 ml

HARUS DENGAN RESEP DOKTER

Manufactured and Released by
Patheon Italia S.p.A., Ferentino - Italy
for Bracco Imaging S.p.A, Milano – Italy

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