iomeron®
iomeprol

Scientific Collection 08

Choice of contrast medium in patients with impaired renal function undergoing percutaneous coronary intervention

Contrast Media and Nephrotoxicity Following Coronary Revascularization by Angioplasty (CONTRAST) Trial

HR Wessely, T Koppara, C Bradaric, M Vorpahl, S Braun S Schulz, J Mehilli, A Schömig, A Kastrati

Circ Cardiovasc Intervent 2009; **2**: 430–437

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Original article:

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A point of view on the CONTRAST study

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IOMERON®: CORE SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product. IOMERON 150 mg/ml Solution for Injection. **IOMERON 200** mg/ml Solution for Injection. **IOMERON 250** mg/ml Solution for Injection. **IOMERON 300** mg/ml Solution for Injection. **IOMERON 350** mg/ml Solution for Injection. **IOMERON 400** mg/ml Solution for Injection.

2. Qualitative and Quantitative Composition IOMERON 150 contains (quantity/100 ml): Active ingredient: Iomeprol: 30.62 g. **IOMERON 200** contains (quantity/100 ml): Active ingredient: Iomeprol: 40.82 g. **IOMERON 250** contains (quantity/100 ml): Active ingredient: Iomeprol: 51.03 g. **IOMERON 300** contains (quantity/100 ml): Active ingredient: Iomeprol: 61.24 g. **IOMERON 350** contains (quantity/100 ml): Active ingredient: Iomeprol: 71.44 g. **IOMERON 400** contains (quantity/100 ml): Active ingredient: Iomeprol: 81.65 g. For excipients see 6.1

3. Pharmaceutical Form Solution for injection displaying the following physicochemical characteristics by Iodine Strengths as below

Iodine concentration MgI/mL	Osmolality MosmL/kg water (x ± s.t95)*	Viscosity MPa.s (x ± s.t95)	
	37°C	20°C	37°C
150	301 ± 14	2.0 ± 0.2	1.4 ± 0.1
200	362 ± 17	3.1 ± 0.2	2.0 ± 0.2
250	435 ± 20	4.9 ± 0.4	2.9 ± 0.3
300	521 ± 24	8.1 ± 0.7	4.5 ± 0.4
350	618 ± 29	14.5 ± 1.1	7.5 ± 0.6
400	726 ± 34	27.5 ± 2.3	12.6 ± 1.1

*Vapour tension method

4. Clinical Particulars

4.1 Therapeutic indications This medicinal product is for diagnostic use only Iomeron 150 Infusion urography, digital substraction phlebography, CT (brain and body) cavernosography, intravenous and intraarterial DSA, ERCP, MCU, MCU in paediatrics. Iomeron 200 Peripheral phlebography, digital subtraction phlebography, CT (brain and body), cavernosography, intravenous and intraarterial DSA, ERCP, arthrography, hysterosalpingography, cholangiography, retrograde urethrography, retrograde pyelo-ureterography, myelography. Iomeron 250 Intravenous urography, peripheral phlebography, CT (brain and body), intravenous and intraarterial DSA, myelography. Iomeron 300 Intravenous urography (in adults and paediatrics), peripheral phlebography, CT (brain and body), cavernosography, intravenous DSA, conventional angiography, intraarterial DSA, angiocardiography (in adults and paediatrics), conventional selective coronary arteriography, interventional coronary arteriography, ERCP, arthrography, hysterosalpingography, fistulography, discography, galactography, cholangiography, dacryocystography, sialography, retrograde urethrography, retrograde pyelo-ureterography, myelography. Iomeron 350 Intravenous urography (in adults and paediatrics), CT (body), intravenous DSA, conventional angiography, intraarterial DSA, angiocardiography (in adults and paediatrics), conventional selective coronary arteriography, interventional coronary arteriography, arthrography, hysterosalpingography, fistulography, galactography, retrograde cholangiography, dacryocystography, sialography. Iomeron 400 Intravenous urography (in adults including those with renal impairment or diabetes), CT (body), conventional angiography, intraarterial DSA, angiocardiography (in adults and paediatrics), conventional selective coronary arteriography, interventional coronary arteriography, fistulography, galactography, dacryocystography, sialography. CT: Computed Tomography, DS: Digital Subtraction, DSA: Digital Subtraction Angiography, ERCP: Endoscopic Retrograde Cholangio-Pancreatography, MCU: Micturating Cisto-Urethrography.

4.2 Posology and method of administration **Instructions for use:** Dosage and rate of administration may vary depending on the clinical question, the technique to be employed, the body area to be examined, the instrumentation, as well as on the age, body size, cardiac output and patient's clinical conditionsIn the CNS the imaging window has been shown to be up to 60 minutes after the administration. In the liver delayed imaging can be performed between 40 and 120 minutes following the injection, depending on the individual imaging needs.

Indication	Formulation mg (iodine)/ml	Proposed dosages
Intravenous urography	250, 300, 350, 400	Adults: 50–150 ml; Newborns: 3–4.8 ml/kg Infants: 2.5–4 ml/kg; Paediatric patients: 1–2.5 ml/kg[a]
Infusion urography	150	Adults: 250 ml Paediatric patients[a]
Peripheral phlebography	200, 250, 300	Adults: 10–100 ml. repeat as necessary[b] (10–50 ml upper extremities; 50–100 ml lower extremities)
Phlebography in DS	150, 200	Adults: 10–100 ml. repeat as necessary[b] (10–50 ml upper extremities; 50–100 ml lower extremities)
CT brain	150, 200, 250, 300	Adults: 50–200 ml; Paediatric patients[a]
CT body	150, 200, 250, 300, 350, 400	Adults: 100–200 ml; Paediatric patients[a]
Cavernosography	150, 200, 300	Adults: up to 100 ml
Intravenous DSA	250, 300, 350, 400	Adults: 100–250 ml; Paediatric patients[a]
Conventional angiography		
Arteriography of upper extremities:	300, 350	Adults[b]
Arteriography of pelvis and lower extremities	300, 350, 400	Adults[b]
Abdominal arteriography:	300, 350, 400	Adults[b]
Arteriography of descending aorta:	300, 350	Adults[b]
Pulmonary angiography:	300, 350, 400	Adults: up to 170 ml
Cerebral angiography:	300, 350	Adults: up to 100 ml
Paediatric arteriography:	300	Children: up to 130 ml[a]
Interventional:	300, 350, 400	Adults[b]; Paediatric patients[a]
Intraarterial DSA		
Cerebral:	150, 200, 300, 350	Adults: 30–60 ml for general view; 5–10 ml for selective injections; Paediatric Patients[a]
Thoracic:	200, 300	Adultsb: 20–25 ml (aorta) repeat as necessary 20 ml (bronchial arteries)
Aortic arch:	150, 200, 300, 350	Adults[c]
Abdomen:	150, 200, 250, 300	Adults[c]
Aortography	150, 200, 300, 350	Adults[c]
Translumbar aortography	150, 200, 300	Adults[b]
Peripheral arteriography:	150, 200, 250, 300	Adults: 5–10 ml for selective injections up to 250ml; Paediatric patients[a]
Interventional:	150, 200, 300	Adults: 10–30 ml for selective injections up to 250ml
Angiocardiography	300, 350 ,400	Adults[b]; Paediatric patients[a]
Conventional selective coronary arteriography	300, 350, 400	Adults: 4–10 ml artery repeat as necessary
ERCP	150, 200, 300	Adults: up to 100 ml
Arthrography	200, 300, 350	Adults: up to 10 ml per injection
Hysterosalpingography	200, 300, 350	Adults: up to 35 ml
Fistulography	300, 350, 400	Adults: up to 100 ml
Discography	300	Adults: up to 4 ml
Galactography	300, 350, 400	Adults: 0.15–1.2 ml per injection
Dacryocystography	300, 350, 400	Adults: 2.5–8 ml per injection
Sialography	300, 350, 400	Adults: 1–3 ml per injection
MCU	150 150	Adults: 100–250 ml Paediatric patients: 40–210 ml[a]
Retrograde cholangiography	200, 300, 350	Adults: up to 60 ml
Retrograde ureterography	200, 300	Adults: 20–100 ml
Retrograde	200, 300 pyelo-ureterography	Adults: 10–20 ml per injection
Myelography	200, 250, 300	Adults: 200: 13–22 ml, 250:

a = According to body weight and age
b = Do not exceed 250 ml. Single injection volume depends on the vascular area to be examined
c = Do not exceed 350 ml

4.3 Contra-indications Hypersensitivity to the active principle and to any of its ingredients. **Intravascular administration** There are no precise and absolute contraindications to the use of non-ionic uroangiographic contrast media. Investigations of the female genitalia are contraindicated in suspected or confirmed pregnancy and in cases of acute inflammation. **Intrathecal administration** Concomitant administration of Iomeprol with corticosteroids is contraindicated (see 4.5 Interactions). Due to overdose considerations, immediate repeat myelography in the event of technical failure is contraindicated.

4.4 Special warnings and special precaution for use SPECIAL WARNINGS General for all administration routes: Consideration of possible serious side effects, the use of iodinated contrast media should be limited to cases for which there is a precise need for a contrast examination. The need should be evaluated on the basis of the clinical status of the patient, in particular in relation to history of pathologies of the cardiovascular, renal and/or hepatobiliary systems. The use of contrast media should be avoided in case of Waldenstroem's paraproteinemia, and multiple myeloma and of advanced hepato and/or renal diseases. Cardioangiographic diagnostic procedures that involve the use of any radiopaque contrast media should be carried out in Hospitals where appropriate emergency facilities and personnel trained in life support is readily available. After any other contrast-enhanced X-ray procedures, competent personnel and adequate emergency facilities should be available (AMBU, oxygen, antihistaminics, vasoconstrictors, cortisonics, etc.) in the radiology departments of public or private clinics. After any other contrast-enhanced X-ray procedures, competent personnel and adequate emergency facilities should be available (AMBU, oxygen, antihistaminics, vasoconstrictors, cortisonics, etc.) in the radiology departments of public or private clinics. Special care should be taken in patients with suspected thrombosis, phlebitis, severe ischemia, local infection or artero-venous obstruction. **Use in specific patients: Neonates, infants, children.** Young infants (age < 1 year) especially neonates, are particularly susceptible to electrolyte imbalances and haemodynamic alterations. Care should be taken regarding the dosage to be used, the details of the procedure and the patient's status. **Elderly.** The elderly are at special risk of reactions due to CM high dosage. Myocardial ischemia, major arrhythmias and extrasystoles are more likely to occur in these patients. The frequently encountered combination of neurological disturbances and severe vascular pathologies constitutes a serious complication. The probability of acute renal insufficiency is higher in these subjects. **Women Of Child-Bearing Potential:** Appropriate investigations and measures should be taken when exposing women of child-bearing potential to any X-ray examination, whether with or without contrast medium. **Use in patients with specific pathologic conditions. Hypersensitivity to iodinated contrast media**. Hypersensitivity or a previous history of a reaction to iodinated contrast media also increases the risk of recurrence of a severe reaction with non ionic media. **Allergic disposition**. It is generally agreed that adverse reactions to iodinated contrast media are more common in patients having a history of allergy: hay fever, hives and food allergy. **Asthmatic patients**. The risk of bronchospasm, inducing reactions in asthmatic patients, is higher after contrast. **Hyperthyroidism, nodular goitre**. The small amount of free inorganic iodide that may be present in contrast media, might have some effects on thyroid function: these effects appear more evident in patients with hyperthyroidism or goitre. Thyroid storms have been reported following administration of ionic contrast media. **Intraarterial and intravenous administration. Use in patients with specific pathologic conditions. Renal failure**. Pre-existing renal impairment may predispose to acute renal dysfunction following contrast media administration. Preventive measures include: identification of high risk patients; ensuring adequate hydration before CM administration, preferably by maintaining i.v. infusion before and during the procedure and until the CM has been cleared by the kidneys; avoiding whenever possible, the administration of nephrotoxic drugs or major surgery or procedure such as renal angioplasty, until the CM has been cleared; postponing a new contrast agent examination until renal function returns to pre-examination levels. Patients on dialysis may receive CM, such as iomeprol, before dialysis.**Diabetes mellitus.** The presence of renal damage in diabetic patients is one of the factors predisposing to renal impairment following CM administration. This may precipitate lactic acidosis in patients who are taking biguanides. As a precaution, biguanides should be stopped 48 hours prior to the CM examination and reinstated only after control of renal function has been regained. **Multiple myeloma, paraproteinaemia (Waldestroem's paraproteinemia)**. It is necessary to consider that the presence of myelomatosis or paraproteinaemias is a factor predisposing to renal impairment following CM administration. Adequate hydration and monitoring the renal function are recommended. **Phaeochromocytoma**. These patients may develop severe (rarely uncontrollable) hypertensive crises following intravascular CM-usage during radiological procedures. **Sickle Cell Disease**. Contrast media may promote sickling in individuals who are homozigous for sickle cell disease. Adequate hydration is recommended. **Myasthenia Gravis.** The administration of iodinated contrast media may aggravate myasthenia signs and symptoms. Severe liver and renal dysfunctions. It is necessary to consider that a combination of severe hepatic and renal impairment can delay CM excretion, therefore predisposing to untoward reactions. **Severe cardiovascular disease.**There is an increased risk of severe reactions in individuals with severe cardiac disease and particularly in those with heart failure and coronary artery disease. The intravascular CM injection may precipitate pulmonary oedema in patients with manifest or incipient heart failure, whereas CM administration, in pulmonary hypertension and heart valvular diseases, may lead to pronounced haemodynamic changes. Ischaemic ECG changes and major arrhythmias are commonest in elderly patients and in those with preexisting cardiac disease: their frequency and severity appear to be related to the severity of cardiac impairment. Severe and chronic hypertension may increase the risk of renal damage following CM administration and the risks associated with the catheterisation procedure. **CNS disorders.** Particular care should be paid to the intravascular administration of CM in patients with acute cerebral infarction, acute intracranial haemorrhage, and conditions involving blood-brain-barrier (BBB) damage, brain oedema and acute demyelination. The presence of intracranial tumors or metastases and a history of epilepsy may increase the probability of the occurrence of convulsive seizures. Neurological symptoms due to degenerative, inflammatory or neoplastic cerebrovascular pathologies may be exacerbated by CM administration. Vasospasm and consequent cerebral ischaemic phenomena may be caused by intravascular injections of CM, often procedurally related and possibly triggered by the tip of the catheter or excess of catheter pressure. Patients with symptomatic cerebrovascular diseases, recent stroke or frequent TIA (transient ischaemic attack) have an increased risk of transient neurological complications. **Alcoholism.** Acute and chronic alcoholism have been proven both experimentally and clinically to increase BBB permeability. This facilitates the passage of iodinated agents into the cerebral tissue, possibly leading to CNS disorders. Caution must be exercised in alcoholics because of the possibility of a reduced seizure threshold. **Drug addiction.** Caution must be exercised in drug addicts because of the possibility of a reduced seizure threshold. Keep away of reach of children. **Special Precautions for use In relation to the patient. Hydration:** Any severe disorders of water and electrolyte balance should be corrected. Especially in patients with multiple myeloma, diabetes mellitus, polyuria, oliguria, hyperuricemia, as well as in babies, small children and elderly patients adequate hydration must be ensured before examination. **Dietary advice:** Unless otherwise instructed by the doctor, a normal diet may be maintained on the day of the examination. Adequate fluid intake must be ensured. However, it is advised that the patient should refrain from eating for two hours prior to the procedure. **Pre- medication:** In patients with phaeochromocytoma pre-medication with alpha-receptor blockers is recommended because of the risk of blood pressure crises. **Hypersensitivity:** In patients with an allergic disposition, known hypersensitivity to iodinated contrast media and a history of asthma, pre-medication with anti-histamines and/or corticoids is recommended to prevent possibile anaphylactoid reactions. **Anxiety:** Pronounced states of excitement, anxiety and pain can be the cause of side effects or intensify contrast-related reactions. These patients may be given a sedative. **Concomitant Treatments:** Treatment with drugs that lower the seizure threshold such as neuroleptics, analgesics, anti-emetics, and phenotiazine derivatives should be discontinued 48 hours before the examination. Treatment should not be resumed until 24 hours post-procedure. Anticonvulsant therapy must not be discontinued and should be administered in optimal dosage. **In relation to the procedure. Coagulation, flushing of catheters.** A property of non-ionic contrast media is the extremely low interference with normal physiological functions. Non-ionic contrast media have less anti-coagulant activity in-vitro than ionic contrast media. Medical personnel performing vascular catheterisation 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, including catheter flushing with physiological saline solution (if necessary with heparin added). **Observation of the patient. Intravascular administration** of contrast media should, if possible, be done with the patient lying down. The patient should be kept under close supervision for 15 minutes following the injection as the majority of severe reactions occur at this time. **Intrathecal administration**. After completion of direct cervical or lumbo-cervical procedures: •raise the head of table steeply (45° angle) for about two minutes to restore CM to lower levels, •raise head of stretcher to at least 30° before moving patient into it; avoid excessive and particularly active patient movement or straining; •maintain the patient under close observation, quiet and in a "head up" position, especially in the first few hours; •the patient should remain supine and at bed rest during this period; •encourage oral fluids and diet as tolerated. **Pre-testing.** Sensitivity test doses are not recommended since severe or fatal reactions to contrast media are not predictable from a patient's history or a sensitivity test. **Extravasation:** Extreme caution during injection of contrast media is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

4.5 Interaction with other medicinal products and other forms of interaction Epidural and intrathecal corticosteroids should never be concurrently administered when iodinated contrast media are used, because corticosteroids may promote and affect the signs and symptoms of arachnoiditis. (see 4.3 Contraindications) **Thyroid function tests.** Following administration of iodinated contrast media, the capacity of the thyroid tissue to take up radioisotopes for the diagnosis of thyroid disorders is reduced for up to two weeks, or even longer in individual cases. The results of Protein Binding Iodine and radioactive iodine uptake studies, which depend on iodine estimations, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected. **Oral Cholecystographic Agents.** Recent literature has revealed no evidence of interactions of renally-excreted contrast media with oral cholecystographic contrast media. **Laboratory tests.** High concentrations of contrast media in serum and urine can interfere with laboratory test results of bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium, phosphate).

4.6 Pregnancy and lactation Animal studies do not indicate any teratogenic or foetotoxic effects. As with other non-ionic contrast media, there are no adequate and well-controlled studies in pregnant women to confirm no harmful effect also in human beings. Whenever possible, radiation exposure, either with or without contrast media use, should be avoided during pregnancy and its benefit accurately weighted against the possible risks. Iodinated contrast media are poorly excreted in human breast milk, and from experience it appears there should be no damage to the breast-fed baby. However, as a cautionary measure, breast-feeding should be discontinued prior to the administration of iomeprol and should not be recommenced until at least 24 hours after the administration of the contrast medium.

4.7 Effects on ability to drive and use machines No data is available. However, given the rare possibility of delayed adverse reactions to contrast media, driving or using machinery should be avoided for 24 hours following the administration.

4.8 Undesirable effects General The use of iodinated contrast media may cause untoward side effects. They are usually mild to moderate. However, more serious reactions up to anaphylactoid shock, with possible fatal outcome, may occur. In most cases reactions occur within minutes of dosing up. However, reactions may manifest also later on up to 24 hours from the injection, depending on the administration route. **Anaphylaxis** (anaphylactoid/hypersensitivity reactions) may manifest with various symptoms, and rarely does any one patient develop all the symptoms. Typically, in 1 to 15 min (but rarely after as long as 2 h), the patient complains of feeling abnormal, agitation, flushing, feeling hot, sweating increased, dizziness, lacrimation increased, rhinitis, palpitations, paraesthesia, pruritus, head throbbing, pharyngolaryngeal pain and throat tightness, dysphagia, cough, sneezing, urticaria, erythema, and mild localised oedema or angioneurotic oedema and dyspnoea owing to tongue and laryngeal oedema and/or laryngospasm manifesting with wheezing and bronchospasm. Nausea, vomiting, abdominal pain, and diarrhoea are less common. These reactions, which can occur independently of the dose administered or the route of administration, may represent the first signs of circulatory collapse. Administration of the contrast medium must be discontinued immediately and, if needed, appropriate specific treatment urgently initiated via venous access. Severe anaphylactic reactions involving the cardiovascular system, such as vasodilatation, with pronounced hypotension, reflex 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. **From Clinical Studies** Adverse experiences reported among patients treated with Iomeprol during clinical trials are shown below.

COMMON. Nervous System: Asthenia, syncope, headache. **Gastrointestinal system:** Nausea **Respiratory system:** Dyspnoea, nasal congestion, laryngeal oedema. **General:** Injection site warmth and pain, pallor.

UNCOMMON. Cardiovascular (mainly after cardio-vascular procedures/interventions): Bradycardia, tachycardia, hypertension, hypotension. **Nervous System:** Dizziness, paralysis, agitation. **Gastrointestinal system:** Vomiting. **Skin and Subcutaneous Tissue:** Wheals, pruritus, rash. **General:** Back pain, chest pain, rigors, injection site haemorrhage, pyrexia, sweating increased.

RARE. Cardiovascular (mainly after cardio-vascular procedures/interventions): Vasodilatation, cyanosis, circulatory collapse. **Nervous System:**Tremor, muscle spasms, confusion, loss of consciousness, visual field defect, aphasia, convulsions, coma. **General:** Anaphylactoid reaction (characterized by cardio-vascular,respiratory and cutaneous symptoms) **Renal and Urinary Disorders:** Renal insufficiency, oliguria, proteinuria, blood creatinine increased.

Some of these events may occur as a consequence of the procedure. Post Marketing Surveillance. The following undesirable effects have been reported during post- marketing in <3/10.000 patients. Intravascular and intra-thecal administration: •**General:** shock, malaise, fatigue, hot flushes, flushing, cold sweat, coldness local, taste abnormality, thirst, injection site reaction. • **Nervous system:** hyperkinetic syndrome, encephalopathy, paralysis, oculomotor nerve paralysis, paraesthesia, dysarthria, dizziness, dysphonia,faecal incontinence, brain oedema, •**Cardiovascular:** cardiac arrest, myocardial infarction, angina pectoris, extrasystoles, arrhythmia, ventricular or atrial fibrillation, tachycardia, palpitations, atrioventricular block, electrocardiogram abnormal, ST segment elevation. • **Respiratory:** respiratory arrest, pulmonary oedema, acute respiratory distress syndrome (ARDS), bronchospasm, asthma, pharyngeal oedema, laryngeal stridor, rhinitis, cough, hyperventilation, hypoxia, pharynx and/or laryngeal discomfort. •**Skin and subcutaneous tissue disorders:** angioneurotic oedema, eczema, urticaria, wheals •cold sweat., •**Vascular (extracardiac):** cerebrovascular disorder, transient ischaemic attack.- Gastrointestinal disorders: pancreatitis acute, ileus, diarrhea, abdominal pain, salivary hypersecretion, dysphagia. • **Urogenital:** urinary incontinence, blood urea increased. •**Senses:** parosmia •Eye disorders: blindness transient, visual disturbance, conjunctivitis, lacrimation increased, photopsia, photophobia.•Musculoskeletal: arthralgia, muscle stiffness. •**Psychiatric disorders:** amnesia, anorexia, anxiety, somnolence. •**Liver and biliary system:** liver function tests abnormal. •**Platelets, bleeding and coagulation:** thrombocytopenia. Administration to body cavities Blood amylase increase is common following ERCP (Endoscopic retrograde cholangiopancreatography). Rare cases of pancreatitis have been described. The reactions reported in cases of arthrography and fistulography usually represent irritative manifestations superimposed on pre-existing conditions of tissue inflammation. Generalised hypersensitivity reactions are rare, generally mild and in the form of skin reactions. However, the possibility of severe anaphylactoid reactions cannot be excluded. (see beginning of chapter 'Undesirable effects'). As with other iodinated contrast media, pelvic pain and malaise may occur after hysterosalpingography.

4.9 Overdose Overdose may lead to life-threatening adverse effects mainly through effects on the pulmonary and cardiovascular system. Treatment of overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy. Iomeprol does not bind to plasma or serum proteins and is therefore dialysable. If needed, hemodialysis can be used to eliminate iomeprol from the body. If intracranial entry of the medium occurs, prophylactic anticovulsant treatment with diazepam or barbiturates orally for 24 to 48 hours should be considered.

5. Pharmacological Properties

5.1 Pharmacodynamic properties Pharmacotherapeutic category: Radiological contrast media: hydrosoluble, nephrotropic, low osmolality. ATC code: V08AB10. The active ingredient of Iomeron formulations is iomeprol, N,N'-bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)-methylamino]-2,4,6-tri-iodo-1,3-benzenedicarboxamide, a tri-iodinated, non-ionic contrast agent, and is indicated for use in X-ray examinations.

5.2 Pharmacokinetic properties Intravascular Administration The pharmacokinetic, tolerability and diagnostic efficacy of Iomeprol in solutions containing up to 400 mg iodine/mL have been determined in healthy volunteers and patients requiring urographic, angiographic, computed tomography (CT) and body cavity examinations. There were no clinically significant changes in laboratory test values and vital signs. The pharmacokinetic of Iomeprol, for intravascular administration, when described by a two-compartment model, shows a rapid phase for drug distribution and a slower phase for drug elimination. In healthy volunteers the mean half-lives of the distribution and elimination phases of Iomeprol were 23 14 (s) min and 109 20 (s) min, respectively. Iomeprol is excreted mainly through the kidneys following intravascular administration. In the absence of renal dysfunction, the cumulative urinary excretion of iomeprol, expressed as percentage of administered intravenous dose, is approximately 24 to 34% at 60 minutes, 84% at 8 hours, 87% at 12 hours, and 95% in the 24 to 96 hour period after administration. In patients with impaired renal function, the elimination half-life is prolonged dependent upon the degree of impairment. Iomeprol does not bind to serum or plasma proteins. Intra-thecal Administration The pharmacokinetics of iomeprol after intra-thecal administration shows that Iomeprol is completely absorbed from the cerebrospinal fluid about 3 to 6 hours. The half-life of elimination is between 8 to 11 hours and is independent from the dose. Plasma concentrations were quantifiable up to 24 hours in 93% of the patients. It is completely excreted from the body through the kidney as unchanged Iomeprol. The majority of urinary excretion occurs in the first 24 hours post-dose, with smaller percentage excreted during the 24-48 hour period.

5.3 Preclinical safety data Pre-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction. Results from studies in rats, mice and dogs demonstrate that iomeprol has an acute intravenous or intra-arterial toxicity similar to that of the other non-ionic contrast media, as well as a good systemic tolerability after repeated intravenous administrations in rats and dogs. LD50 of iomeprol in g (Iodine)/kg and the relevant 95% confidence limits in animals are as follows: Intravenous administration: 19.9 (19.3-20.5) (mouse); 14.5 (13.2-16.0) (rat); > 12.5 (dog) Intraperitoneal administration: 26.1 (23.3-29,2) (mouse); 10 (8.9-11.3) (rat); Intracerebro-ventricular administration: 1.4 (1.3-1.6) (mouse); Intracisternal administration: >1.2 (rat) Intracarotid administration: 5.8 (4.64-7.25) (rat)

6. Pharmaceutical Particulars

6.1 List of excipients Trometamol, hydrochloric acid (d=1.18), water for injection

6.2 Incompatibilities Contrast media must not be mixed with other medicinal products, to avoid eventual incompatibilities.

6.3 Shelf life 5 years

6.4 Special precautions for storage Expiry date refers to the product stored correctly in intact packaging. Protect from light. Although the sensitivity of iomeprol to X-rays is low, it is advisable to store the product out of reach of ionizing radiation. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the solution if it is discolored or particulate matter is present.

6.5 Nature and contents of container Type I or Type II glass vials or bottles with halobutyl stoppers and an aluminium crimp seal.

6.6 Instruction for use/handling Vial or bottles containing contrast media solution are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. The use of proper withdrawal cannulae for piercing the stopper and drawing up the contrast medium is recommended. The contrast medium should not be drawn into the syringe until immediately before use and should not be diluted. Solutions not used in one examination session or waste material, such as the connecting tubes, should be disposed. Any residue of contrast medium in the syringe must be discarded. Bottles of 500 ml should be used in conjunction with an injector system. After each patient examination, the connecting tubes (to the patient) and relevant disposable parts should be disposed because could be contaminated with blood. At the end of the sessions, the left over solution in the bottle and in the connecting tubes as well as any disposable parts of the injector system should be discarded. Any additional instructions from the respective equipment manufacturer must also be adhered to.

7. Marketing Authorisation Information The Marketing Authorisation Holder, Number, and Date of Approval may be different in different Countries. Volumes, presentations, and indications may also differ. Refer to Local Summary of Product Characteristics. Please contact Bracco Imaging SpA – Via Egidio Folli, 50 20134 Milano- Italy for further information.

8. Date of Preparation of this Document: April 2009

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