Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Iomeron 350 mgI/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains 71.44 w/v of concentration of iomeprol equivalent to 35 % iodine or 350 mg iodine/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

A clear, colourless solution supplied in Type I or Type II glass bottles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

X-ray contrast medium used for:
peripheral arteriography
venography
aortography
angiocardiography and left ventriculography
coronary arteriography
visceral arteriography
digital subtraction angiography
computed tomography enhancement
urography
arthrography
dacryocystrography
sialography
fistulography
galactography

4.2 Posology and method of administration

Peripheral arteriography	adults children	10 - 90ml * * *
Venography	adults	10 - 100ml* (max 250ml) 10 - 50ml upper extremity 50 - 100ml lower extremity
Aortography	adults children	50 - 80ml * *
Angiocardiography and left ventriculography	adults children	30 - 80ml (max 250ml) * *
Coronary arteriography	adults	4 - 10ml per artery *
Visceral arteriography	adults children	5 - 50ml* or according to type of examination (max 250ml) * *
Digital Subtraction Angiography intravenous	adults	30 - 60ml* (max 250ml)

Computed Tomography • CT brain • CT body	 adults children adults children	 50 - 150ml * * 40 - 150ml (max 250ml) * *
Urography • intravenous	 adults neonates babies children	 50 - 150ml 3 - 4.8ml/kg 2.5 - 4ml 1 - 2.5ml/kg or *
Arthrography	adults	up to 10ml
Dacryocystography	adults	3 - 8ml
Sialography	adults	1 - 3ml
Fistulography	adults	1 - 50ml
Galactography	adults	0.2 - 1.5ml

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

In elderly patients the lowest effective dose should be used.
Unless otherwise instructed by the doctor, a normal diet may be maintained on the day of the examination.

Intravascular administration should be performed if possible with the patient lying down. The patient should be kept in this position and closely observed for 30 minutes after the procedure since the majority of severe incidents occur with this time.

4.3 Contraindications

Hypersensitivity to the active substance 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.

Hypersensitivity
In patients with suspected or known hypersensitivity to contrast media, sensitivity test doses are not recommended, as severe or fatal reactions to contrast media are not predictable from sensitivity test.
A positive history of allergy, asthma or untoward reaction during previous similar investigations indicates a need for extra caution since, as with other contrast media, this product may provoke anaphylaxis or other manifestations of allergy with nausea, vomiting, dyspnoea, erythema, urticaria and hypotension. The benefits should clearly outweigh the risks in such patients and appropriate resuscitative measures should be immediately available. The primary treatments are as follows:

Effect	Major Symptoms	Primary Treatment
Vasomotor effect	warmth nausea/vomitting	reassurance
Cutaneous	scattered hives severe uticaria	H_1 -antihistamines H_2 -antihistamines
Bronchospastic	Wheezing	oxygen
Anaphylactoid reaction	 Angioedema uticaria bronchospasm hypotension	Beta-2-agonist inhalers oxygen iv fluids adrenergics (ivepinephrine) Inhaledbeta-2-adrenergics antihistamines (H_1-and H_2 -blockers) corticosteroids

Hypotensive Vagal reaction	hypotension hypotension bradycardia	iv fluids iv fluids iv atropine

From Bush WH The Contrast Media Manual
Katzburg RW Ed. Williams and Wilkins
Baltimore 1992 Chapter 2 p23

Patients using beta-adrenergic blocking agents, particularly asthmatic patients, may have a lower threshold for bronchospasm and are less responsive to treatment with beta agonists and adrenaline, which may necessitate the use of higher doses of adrenaline.

Angiography
Electrocardiograms and vital signs should be routinely monitored throughout Angiocardiography, ventriculagraphy, selective coronary arteriography.
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 a syringe, and intravascular catheters should be flushed frequently to minimise the risk of clotting which, rarely, has led to serious thromboembolic complications.

Risk of inflammation and extravasation
Extreme caution during injection of contrast media is necessary to avoid extravasation.

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 kidney, 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.

Cardiac diseases
Care should be taken in severe cardiac disease particularly heart failure and coronary artery disease. Reactions may include pulmonary oedema, haemodynamic changes, ischaemic ECG changes and arrhythmias.

Renal impairment
Preexisting renal impairment may predispose to acute renal dysfunction following contrast media administration.
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.

In patients with moderate to severe impairment of renal function, attention should be paid to renal function parameters before re-examining the patient with a contrast medium.

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.

Thyroid function and thyroid function tests
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 latent or overt hyperthyroidism or goitre. Hyperthyroidism or even thyroid storms have been reported following administration of iodinated contrast media.
Use may interfere with thyroid function tests.

Neurological symptoms

Particular care is needed in patients with acute cerebral infarction, acute intracranial haemorrhage and any conditions involving damage to the blood brain barrier, brain oedema or acute demyelination. Convulsive seizures are more likely in patients with intracranial tumours or metastases or with a history of epilepsy.

Neurological symptoms related to cerebrovascular diseases, intracranial tumours/metastases or degenerative, ischaemic or inflammatory pathologies may be exacerbated. These patients have an increased risk of transient neurological complications.

Vasospasm and consequent cerebral ischaemic phenomena may be caused by intravascular injection.
Anticonvulsant therapy should not be discontinued.

In acute and chronic alcoholism the increase in blood brain barrier permeability facilitates the passage of the contrast medium into cerebral tissue possibly leading to CNS disorders. There is a possibility of a reduced seizure threshold in alcoholics.

In patients with a drug addiction there is also the possibility of a reduced seizure threshold.

Contrast induced encephalopathy

Encephalopathy has been reported with the use of iomeprol (see section 4.8).
Contrast encephalopathy 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 of iomeprol, and generally resolves within days.
The product should be used with caution in patients with conditions that disrupt the integrity of the blood brain barrier (BBB), potentially leading to increased permeability of contrast media across the BBB and increasing the risk of encephalopathy. If contrast encephalopathy is suspected, administration of iomeprol should be discontinued and appropriate medical management should be initiated.

Severe cutaneous adverse reactions

Severe cutaneous reactions (SCARs) including Steven-Johnson (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with the intravascular administration of iodinated contrast agents (see Section 4.8). At the time of administration patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear Iomeron should be stopped immediately. If the patient has developed a serious reaction such as SJS, TEN, AGEP or DRESS with the use of Iomeron, administration of Iomeron must not be restarted to this patient at any time.

Myasthenia gravis

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

Phaeochromocytoma

Patients with phaeochromocytoma may develop severe, occasionally uncontrollable hypertensive crises following intravascular contrast media usage during radiological procedures. Premedication with an alpha and beta-receptor blocker is recommended in these patients before intra-arterial injection of contrast media under the supervision of a physician. Pronounced excitement, anxiety and pain can cause side effects or intensify reaction to the contrast medium. A sedative may be given.

Diabetes

Contrast media may cause a transient renal impairment that may precipitate lactacidosis in patients treated with biguanides (see section 4.5).

Paediatric population: Infants up to 1 year, especially the new-born, are particularly susceptible to electrolyte imbalance and haemodynamic alterations. Care should be taken regarding the dosage used.
Hypothyroidism or transient thyroid suppression may be observed after exposure to iodinated contrast media.
Special attention should be paid to paediatric patients below 3 years of age because an incident underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy.
The incidence of hypothyroidism in patients younger than 3 years of age exposed to iodinated contrast media has been reported between 1.3% and 15% depending on the age of the subjects and the dose of the iodinated contrast agent and is more commonly observed in neonates and premature infants. Thyroid function should be evaluated in all paediatric patients younger than 3 years of age following exposure to iodinated contrast media. If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalized.

Elderly: A combination of neurological disturbances and vascular pathologies present a serious complication.

4.5 Interaction with other medicinal products and other forms of interaction

Use of the product may interfere with tests for thyroid function.
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. Any test that might be affected by contrast media should be performed prior to administration of the contrast medium. These findings have not been associated with clinical manifestations.
Vasopressor agents should not be administered prior to iomeprol.

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 in the following scenarios; prior to an intraarterial contrast medium administration with first pass renal exposure, in patients with eGFR less than 30 ml/min/1.73m^2 receiving intravenous contrast medium, or intra-arterial contrast medium with second pass renal exposure, or in patients with acute kidney injury, and re-instated only after 48 hours if renal function has not changed significantly.

Consider the discontinuation of treatment with drugs that lower the seizure threshold until 24 hours post-procedure for intrathecal use and patients with blood-brain barrier disorders (see CNS Disorders under SPC Section 4.4).

Allergy-like reactions to contrast media are more frequent and may manifest as delayed reactions in patients treated with immuno-modulators, like Interleukin-2 (IL-2), and Interferon.

Contrast media may interfere with laboratory tests for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium, and phosphate).

4.6 Fertility, pregnancy and lactation

Fertility
Elective exposure to diagnostic radiation should be restricted as far as possible to the first ten days of the ovulatory cycle.

Pregnancy
Animal studies have not indicated any harmful effects with respect to the course of pregnancy or on the health of the unborn or neonate. The safety of iomeprol in human pregnancy however has not been established. Therefore avoid in pregnancy unless there is no safer alternative.
In neonates who have been exposed to iomeprol *in utero*, it is recommended to monitor thyroid function (see section 4.4).

Breastfeeding
No human data exist concerning the excretion of iomeprol in breast milk. Animal studies have demonstrated that the excretion of iomeprol in breast milk is similar to that of other contrast agents and that these compounds are only minimally absorbed by the gastrointestinal tract of the young. Adverse effects on the nursing infant are therefore 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, severe and life-threatening reactions sometimes leading to death have been reported. In most cases, reactions occur within minutes of dosing but at times reactions may occur at later time.
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 patientcomplains 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 angioedema and dyspnoea owing to tongue and laryngeal oedema and/or laryngospasm manifesting with wheezing and bronchospasm.

Nausea, vomiting, abdominal pain, and diarrhoea are also reported.
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 reactions involving the cardiovascular system, such as vasodilatation, with pronounced hypotension, tachycardia, 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.
The adverse reactions reported in clinical trials among 4,920 adult patients and from post-marketing surveillance are represented in the tables below by frequency and classified by MedDRA system organ class.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adult patients involved in clinical trials with intravascular administration of Iomeprol were 4,739.
Adults

System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1000)**	**Frequency unknown***
Blood and lymphatic system disorders				Thrombocytopenia, Haemolytic anaemia
Immune system disorders				Anaphylactoid reaction
Endocrine disorder				Hyperthyroidism
Psychiatric disorders				Anxiety Confusional state
Nervous system disorders		Dizziness Headache	Presyncope	Coma Transient ischaemic attack Paralysis Syncope Convulsion Loss of consciousness Dysarthria Paraesthesia Amnesia Somnolence Taste abnormality Contrast induced encephalopathy***
Eye disorders				Blindness transient Visual disturbance Conjunctivitis Lacrimation increased Photopsia
Cardiac disorders			Bradycardia Tachycardia Extrasystoles	Cardiac arrest Myocardial infarction Cardiac failure Angina pectoris Arrhythmia Ventricular or atrial fibrillation Atrioventricular block
Vascular		Hypertension	Hypotension	Circulatory collapse or shock

disorders				Flushing Pallor Cyanosis Coronary artery thrombosis Coronary artery embolism Vasospasm**** Ischemia****
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Respiratory arrest Acute respiratory distress syndrome (ARDS) Pulmonary oedema Laryngeal oedema Pharyngeal oedema Bronchospasm Asthma Cough Pharynx discomfort Laryngeal discomfort Rhinitis Dysphonia
Gastrointestinal disorders		Vomiting Nausea		Diarrhoea Abdominal pain Salivary hypersecretion Dysphagia Salivary gland enlargement
Skin and subcutaneous tissue disorders		Erythema Urticaria Pruritus	Rash	Acute generalized exanthematous pustulosis Angioedema Sweating increased Stevens-Johnson's syndrome Toxic epidermal necrolysis Erythema multiforme Drug Reaction with Eosinophilia and Systemic Symptoms
Musculoskeletal and connective tissue disorder			Back pain	Arthralgia
Renal and urinary disorders				Acute kidney injury*****
General disorders and administration site conditions	Feeling hot	Chest pain Injection site warmth and pain	Asthenia Rigors Pyrexia	Injection site reaction** Coldness local Malaise Thirst
Investigations			Blood creatinine increased	Electrocardiogram ST segment elevation Electrocardiogram abnormal

* Since the reactions were not observed during clinical trials with 4,739 patients, best estimate is that their relative occurrence is rare (≥1/10,000 to <1/1000).
The most appropriate MedDRA term is used to describe a certain reaction and its symptoms and related conditions.
** Injection site reactions comprise injection site pain and swelling. In the majority of cases they are due to extravasation of contrast medium. These reactions are usually transient and result in recovery without sequelae. Cases of extravasation with inflammation, skin necrosis and even development of compartment syndrome have been reported.
*** Encephalopathy 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, brain oedema.

****Vasospasm and consequent ischaemia have been observed during intra-arterial injections of contrast medium, in particular after coronary and cerebral angiography often procedurally related and possibly triggered by the tip of the catheter or excess catheter pressure
*****Transient renal failure with oliguria, proteinuria and an increase in serum creatinine may develop, particularly in patients with impaired renal function. In case of extravasal injection a tissue reaction may develop in rare cases.

Paediatric patients
There is limited experience with paediatric patients. The clinical trial paediatric safety database comprises 184 patients.
The Iomeprol safety profile is similar in children and adults.
Transient hypothyroidism may occur in neonates, especially in preterm or low birth weight neonates, and children (0-3 years), when exposed to iomeprol.

Administration to body cavities
After injection of an iodinated contrast media in body cavities, contrast media are slowly absorbed from the area of administration into systemic circulation and subsequently cleared by renal elimination.
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 pre-existing conditions of tissue inflammation.
Hypersensitivity reactions are rare, generally mild and in the form of skin reactions. However, the possibility of severe anaphylactoid reactions cannot be excluded.
As with other iodinated contrast media, pelvic pain and malaise may occur after hysterosalpingography.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The effects of overdose on the pulmonary and cardiovascular systems may become life-threatening. Treatment consists of support of the vital functions and prompt use of symptomatic therapy.

Iomeprol does not bind to plasma or serum proteins and is therefore dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Iomeprol is a low osmolality, non-ionic organic molecule with radio-opacity conferred by an iodine content of 49% of the molecular weight. It is formulated for use as an intravascular/intracavitary contrast medium in concentrations of up to 400mg iodine per ml. Even at this concentration the low viscosity allows delivery of high doses through thin catheters.

5.2 Pharmacokinetic properties

The pharmacokinetics of intravascularly administered iomeprol are similar to those of other iodinated contrast media and conform to a two-compartment model with a rapid distribution and a slower elimination phase. In healthy subjects, the mean distribution and elimination half-lives of iomeprol were 0.37 hours and 1.83 hours respectively.

Distribution volume is similar to that of extra cellular fluid. There is nosignificant serum protein binding and iomeprol is not metabolized.

Elimination is almost exclusively through the kidneys (90% of the dose recovered in the urine within 96 hours of its administration) and is rapid (50% of an intravascularly administered dose within 2 hours).

5.3 Preclinical safety data

There are no pre-clinical data of relevance which are additional to those included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol

Hydrochloric Acid (for pH adjustment)
Water for Injection

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.
For 500 ml bottle: the maximum use time after a bottle stopper has been pierced is 10 hours.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original container.

6.5 Nature and contents of container

Colourless Type I or Type II glass bottles with rubber/aluminium cap.
Quantities of 50, 75, 100, 150, 200, 250 and 500 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before use, examine the product to assure that the container and closure have not been damaged. Do not use the solution if it is discolored or particulate matter is present.

The rubber stopper should never be pierced more than once. The use of proper withdrawal cannulas 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.

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile syringes. Sterile techniques must be used with any spinal puncture or intravascular injection, and with catheters and guidewires. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

500 ml bottles should be used in conjunction with an injector system. After each examination session, the connecting tubes and all disposable parts of the eventual injector system should be discarded. Any additional instructions from the respective equipment manufacturer must also be adhered to.

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

7 MARKETING AUTHORISATION HOLDER

Bracco Imaging spa
via Egidio Folli 50
20134 Milan
Italy

8 MARKETING AUTHORISATION NUMBER

PA1826/006/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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