SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Iomeron 300, solution for injection, multi-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains 61.24% w/v of Iomeprol equivalent to 30% iodine or 300mg iodine/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear colourless to pale yellow solution supplied in glass multi-dose container.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

X-ray contrast medium used for computed tomography enhancement, including CTA (CT Angiography).

4.2 Posology and method of administration

Computed Tomography

brain	adults	50 - 150ml
	children	*
body	adults	40 - 150ml max 250ml

	children	*

*According to body size and age

In elderly patients the lowest effective dose should be used.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

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 reactions, including hypersensitivity or anaphylactic reactions, to the contrast medium itself.

In consideration of possible complications, the patient should be kept under observation for at least 30 minutes after the examination.

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

A normal diet should be maintained until the patient refrains from eating 2 hours before the procedure.

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 (see Section 4.8 for additional information on anaphylaxis reactions). Patients using beta-adrenergic blocking agents may have a lower threshold for bronchospasm, especially if asthmatic, and are less responsive to treatment with beta agonists and adrenaline, which may necessitate the use of higher doses of adrenaline.

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/vomiting	reassurance
Cutaneous	scattered hives severe urticaria	H_1 -antihistamines H_2 -antihistamines

Bronchospastic	wheezing	oxygen Beta-2-agonist inhalers
Anaphylactoid reaction	angioedema urticaria bronchospasm hypotension	oxygen iv fluids adrenergics (iv epinephrine) Inhaled beta-2-adrenergics antihistamines (H_1-and H_2- blockers) corticosteroids
Hypotensive	hypotension	iv fluids
Vagal reaction	hypotension bradycardia	iv fluids iv atropine

From: Bush WH; The Contrast Media Manual; Katzburg RW Ed.; Williams and Wilkins; Baltimore 1992; Chapter 2 p 23

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, liver or myocardium, myelomatosis or other paraproteinaemias, sickle cell disease diabetes mellitus, polyuria, oligouria, hyperuricaemia, neonates, 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.

Cardiovascular diseases

Care should be taken in patients with severe cardiac disease particularly heart failure and coronary artery disease. The intravascular contrast media injection may precipitate pulmonary oedema in patients with manifest or incipient heart failure, whereas in patients with pulmonary hypertension and valvular heart diseases, contrast media administration may lead to pronounced haemodynamic changes,

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.

Myasthenia gravis

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

CNS Disorders and 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 by CM administration. There is an increased risk of transient neurological complications in these patients and those with symptomatic cerebrovascular disease (eg stroke, transient ischaemic attacks).

Vasospasm and consequent cerebral ischaemic phenomena may be caused by intravascular injection of CM.

Anticonvulsant therapy should not be discontinued.

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, potentially leading to increased permeability of contrast media across the blood brain barrier and increasing the risk of encephalopathy. If contrast encephalopathy is suspected, administration of iomeprol should be discontinued and appropriate medical management should be initiated.

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 CMS 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.

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.

Phaeochromocytoma
Patients with phaeochromocytoma may develop severe, occasionally uncontrollable hypertensive crises during intravascular administration. Premedication with an alpha and beta receptor-blocker is recommended in these patients. Pronounced excitement, anxiety and pain can cause side effects or intensify reaction to the contrast medium. A sedative may be given.

Renal failure
In patients with moderate to severe impairment of renal function, attention should be paid to renal function parameters, in particular before re-examining the patient with contrast media.
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 the same level as before the examination.

Contrast media may cause transient renal impairment that may precipitate lactic acidosis in diabetic 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
The elderly are at special risk of reactions due to CM high dosage.
A combination of neurological disturbances and vascular pathologies present a serious complication.

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

4.5 Interaction with other medicinal products and other forms of interaction

Use of the product may interfere with tests for thyroid function.

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.

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).

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).

4.6 Fertility, pregnancy and lactation

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.
Since, wherever possible, exposure to radiation should be avoided during pregnancy, the benefits of any X-ray examination, whether with or without contrast material, should for this reason alone be carefully weighed against the possible risk.
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

General

The use of iodinated contrast media may cause untoward side effects. They 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 patient complains of feeling abnormal, agitation, flushing, feeling hot, sweating increased, dizziness, increased lacrimation, rhinitis, palpitations, paresthesia, pruritus, sore throat and throat tightness, dysphagia, cough, sneezing, urticaria, erythema, mild localised oedema, angioneurotic oedema and dyspnoea due to glottic/laryngeal/pharyngeal oedema and/or spasm 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, 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.
The adverse reactions reported in clinical trials 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

	Adverse Reactions

	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 t o <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 disorders				Hyperthyroidism
Psychiatric disorders				Anxiety Confusional state
Nervous system disorders		Headache Dizziness	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	Cardiac arrest Myocardial infarction Cardiac failure Angina pectoris Arrhythmia Ventricular or atrial fibrillation Atrioventricular block Extrasystoles
Vascular disorders		Hypertension	Hypotension	Circulatory collapse or shock Flushing Pallor Cyanosis Coronary artery thrombosis Coronary artery embolism

System Organ Class	Adverse Reactions			
	Clinical Trials			Post-marketing Surveillance
	Common (≥1/100 t o <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency unknown*
				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		Nausea Vomiting		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

System Organ Class	Adverse Reactions			
	Clinical Trials			Post-marketing Surveillance
	Common (≥1/100 t o <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Frequency unknown*
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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

ATC code: V08AB10

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/intrathecal 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 0.5 hours and 1.9 hours respectively.

Distribution volume is similar to that of extra cellular fluid. There is no significant 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

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 intraarterial 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

trometamol

hydrochloric acid

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

Five years

The maximum use time after a bottle stopper has been pierced is 10 hours.

6.4 Special precautions for storage

Store below 30°C

Protect from light

6.5 Nature and contents of container

Colourless type I or type II glass bottles with chlorobutyl or bromobutyl rubber stopper/aluminium cap containing 500 ml of solution.

Boxes of 1, 5 and 6 bottles.

6.6 Special precautions for disposal

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 stopper should be pierced only once. The use of proper withdrawal cannulas for piercing the stopper and drawing up the contrast medium is recommended.

Multi-dose containers should be used only in conjunction with an automatic injector which has been approved for multipatient use.

After each patient, the connector between the injector and the patient should be replaced. All other devices should be replaced following the injector manufacturer's instructions. In any case, strictly follow the manufacturer's instructions.

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

7. MARKETING AUTHORISATION HOLDER

Bracco UK Ltd
Magdalen Centre
The Oxford Science Park
Oxford, OX4 4GA
United Kingdom

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