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 300 mg 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

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

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.

Hydration
Any severe disorders of water and electrolyte balance must be corrected prior to administration. Adequate hydration must be ensured particularly in patients with diabetes mellitus, polyuria, oliguria and hyperuricaemia; also in babies, small children and the elderly. Rehydration prior to use of Iomeprol is recommended in patients with sickle cell disease.

Special population

Hypersensitivity to iodinated contrast media, allergic predisposition

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/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

The risk of bronchospasm-inducing reactions in asthmatic patients is higher after contrast media administration, especially in patients taking beta-blockers.

Hypersensitivity testing

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.

Myelomatosis or paraproteinaemias are conditions predisposing to renal impairment following CM administration. The benefits of the use of a contrast-enhanced procedure should be carefully weighed against the possible risk. Adequate hydration and monitoring of renal function are recommended after CM administration.

Cardiovascular diseases

Care should be taken in patients with severe cardiac disease particularly heart failure and coronary artery disease. Cardiac manifestations may include pulmonary oedema, haemodynamic changes, ischaemic ECG changes and arrhythmias. In severe, chronic hypertension the risk of renal damage following administration of a contrast medium is increased.

The product should be used with caution in patients with hyperthyroidism or goitre. Use may interfere with thyroid function tests.

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

CNS Disorders

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 or inflammatory pathologies may be exacerbated.

There is an increased risk of transient neurological complications in patients with symptomatic cerebrovascular disease eg stroke, transient ischaemic attacks. 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 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.

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;

A combination of severe hepatic and renal impairment delays excretion of the contrast medium therefore such patients should not be examined unless absolutely necessary.

Diabetes mellitus
Care should be taken in renal impairment and diabetes. In these patients it is important to maintain hydration in order to minimise deterioration in renal function.
The presence of renal damage in diabetic patients is one of the factors predisposing to renal impairment following contrast media administration. This may precipitate lactic acidosis in patients who are taking metformin (see section 4.5 - Interaction with medicaments and other forms of interaction).

Children:
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.
Transient hypothyroidism may occur in neonates when the mother or the neonate has received an iodinated contrast agent. Thyroid function tests (usually TSH and T4) are recommended in neonates 7-10 days and 1 month after exposure to Iomeron especially in preterm neonates.
Elderly:
The elderly are at special risk of reactions due to reduced physiological functions, especially when high dosage of contrast media is used. A combination of neurological disturbances and vascular pathologies present a serious complication. The probability of acute renal insufficiencies is higher in these people.

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.

Treatment with drugs that lower the seizure threshold such as certain neuroleptics (MAO inhibitors, tricyclic antidepressants), analeptics, and anti-emetics and phenothiazine derivatives should be discontinued 48 hours before the examination. Treatment should not be resumed until 24 hours post-procedure.

It has been reported that cardiac and/or hypertensive patients under treatment with diuretics, ACE-inhibitors, and/or beta blocking agents are at higher risk of adverse reactions when administered iodinated contrast media.

Beta-blockers may impair the response to treatment of bronchospasm induced by contrast medium.

Patients with normal renal function can continue to take metformin normally. In diabetic patients with diabetic nephropathy, under treatment with metformin and with moderate renal impairment, metformin should be stopped at the time of, or prior to, the procedure and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal. In emergency patients in whom renal function is either impaired or unknown, the physician shall weigh out risk and benefit of an examination with a contrast medium and take precautions. Metformin should be stopped from time of contrast medium administration. After the procedure the patient should be monitored for signs of lactic acidosis. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

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).

4.6 Fertility, pregnancy and lactation

Women of childbearing 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.

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.

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 4,515.

Adults

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***
Blood and lymphatic system disorders				Thrombocytopenia Haemolytic anaemia
Immune system disorders				Anaphylactoid reaction
Psychiatric disorders				Anxiety Confusional state
Nervous system disorders		Headache Dizziness	Presyncope	Coma Transient ischaemic attack Paralysis Syncope Convulsion Loss of consciousness Dysarthria

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*
				Paraesthesia Amnesia Somnolence Taste abnormality
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 Palpitations Cyanosis
Vascular disorders		Hypertension	Hypotension	Circulatory collapse or shock Hot flush Flushing Pallor
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Respiratory arrest Acute respiratory distress syndrome (ARDS) Pulmonary oedema Laryngeal oedema Pharyngeal oedema Bronchospasm Asthma Cough Hyperventilation 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 Cold sweat Sweating increased
Musculoskeletal and connective tissue disorder			Back pain	Arthralgia
Renal and urinary disorders				Renal failure
General disorders and administration site	Feeling hot	Chest pain Injection site	Asthenia Rigors	Injection site reaction** Coldness local

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*
conditions		warmth and pain	Pyrexia	Fatigue Malaise Thirst
Investigations			Blood creatinine increased	Electrocardiogram ST segment elevation Electrocardiogram abnormal

* Since the reactions were not observed during clinical trials with 4515 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.

As with other iodinated contrast media, very rare cases of mucocutaneous syndromes, including Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome) and erythema multiforme, have been reported following the administration of Iomeprol injection.

Paediatric patients

There is limited experience with paediatric patients. The clinical trial paediatric safety database comprises 167 patients.

The Iomeprol safety profile is similar in children and adults.

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 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.

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

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Oxford, OX4 4GA
United Kingdom

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