1. NAME OF THE MEDICINAL PRODUCT

Iomeron 300, solution for injection

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

X-ray contrast medium used for:

peripheral arteriography
venography
angiogardiography and left ventriculography
cerebral arteriography
visceral arteriography
digital subtraction angiography
computed tomography enhancement
urography
ERCP
dacryocystography
sialography
fistulography
galactography
myelography

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
angiocardiography and left ventriculography	adults children	30 - 80ml max 250ml * *
cerebral arteriography	adults children	5 - 12ml * 3 - 7ml or * *
visceral arteriography	adults children	5 - 50ml* or according to type of examination; max 250ml * *
digital subtraction angiography intra arterial		

visceral	adults	2 - 20ml per artery* aorta 25-50ml* both 250ml max
peripheral	adults	5 - 10ml per artery* max 250ml
intravenous	adults	30 - 60ml* max 250ml
computed tomography		
brain	adults	50 - 150ml
	children	* *
body	adults	40 - 150ml max 250ml
	children	* *
urography intravenous	adults	50 - 150ml
	neonates	3 - 4.8ml/kg
	babies	2.5 - 4ml
	children	1 - 2.5ml/kg or *
arthrography	adults	1 - 10ml
ERCP	adults	12 - 30ml
dacryocystography	adults	3 - 8ml
sialography	adults	1 - 3ml
fistulography	adults	1 - 50ml
galactography	adults	0.2 - 1.5ml
myelography	adults	10 - 15ml by lumbar injection

* 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.

In myelography, lower doses may be used for lumbar or thoracic studies and higher doses for cervical or total columnar studies. Regardless of the nature of the myelographic study, Iomeron should be injected slowly over 1-2 minutes.

The X ray can be taken up to 60 minutes following injection. Post myelographic CT of the spinal column should be delayed for approximately four hours to allow dilution and clearance of excessive contrast.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients. .

Intrathecal concomitant administration of corticosteroids with contrast media is contraindicated.

4.4 Special warnings and special 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.

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 diabetes mellitus, polyuria, oligouria, hyperuricaemia, infants, small children, and elderly patients, should not be exposed to dehydration. Also patients with severely compromised hepatic and renal impairment are more at risk. Caution should be exercised in hydrating patients with underlying conditions that may be worsened by fluid overload, including congestive heart failure.

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 weighted against the possible risk. Adequate hydration and monitoring of renal function are recommended after CM administration.

Cardiovascular 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.

In severe, chronic hypertension the risk of renal damage following administration of a contrast medium is increased. In these cases the risks associated with the catheterization procedure are 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 intra-arterial 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 impairment
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:
There is special risk of reactions involving the circulatory system such that myocardial ischaemia, major arrhythmias and extrasystoles are more likely to occur. A combination of neurological disturbances and vascular pathologies present a serious complication. The probability of acute renal insufficiencies is higher in these people.

Precautions for dedicated exams
Angiography
Non ionic contrast media have less antiocoagulant 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.

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.

Myelography
Following intrathecal use, the patient should rest with the head and the chest elevated for 1 hour and be kept well hydrated. Thereafter, he/she may ambulate carefully, but bending down must be avoided. If remaining in bed, the head and chest should be kept elevated for 6 hours. Patients, suspected of having a lower seizure threshold should be observed during this period.

Venography
Special care is required when venography is performed in patients with thrombosis, phlebitis, severe ischaemic disease, local infection or a totally obstructed artero-venous system.

4.5 Interaction with other medicaments 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 phenotiazine 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).

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 section 4.3 Contraindications).

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.
After intrathecal administration, it is recommended that the patient should wait 24 hours before driving or operating machinery.

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 among 4,903 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.

4.8.1 Intravascular administration

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 Paraesthesia Amnesia Somnolence Taste abnormality
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 Palpitations Cyanosis

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*
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 conditions	Feeling hot	Chest pain Injection site warmth and pain	Asthenia Rigors Pyrexia	Injection site reaction** Coldness local 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.

Coronary artery thrombosis and coronary artery embolism have been reported as a complication of coronary catheterization procedures.

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.

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.

4.8.2 Intrathecal administration

Adults

Adults patients involved in clinical trials with intrathecal administration of Iomeprol were 388.

The most frequently reported adverse reactions following intrathecal administration of Iomeprol are headache, dizziness, nausea, vomiting and back pain. These reactions are usually mild to moderate and transient in nature. Rarely, headache may persist for days. Most side effects occur some hours (3 to 6 hours) after the procedure, due to the distribution of the contrast medium in the CSF circulation from the site of administration to the intravascular space (see section 5.2: Pharmacokinetic properties). Most reactions usually occur within 24 hours after injection.

System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Frequency unknown***
Immune system disorders				Anaphylactoid reaction
Nervous system disorders	Headache	Dizziness	Hypoaesthesia Paraesthesia Paraparesis Loss of consciousness Somnolence	Epilepsy
Vascular disorders		Hypertension	Hypotension Flushing	
Gastrointestinal disorders		Nausea Vomiting		
Skin and subcutaneous tissue disorders			Hyperhidrosis Pruritus	Rash
Musculoskeletal and connective tissue disorder		Back pain Pain in extremity	Musculoskeletal stiffness Neck pain	
General disorders and administration site conditions		Injection site reaction**	Feeling hot Pyrexia	

* Since the reactions were not observed during clinical trials with 388 patients, best estimate is that their relative occurrence is uncommon (≥ 1/1000 to <1/100.

The most appropriate MedDRA term is used to describe a certain reaction and its symptoms and related conditions.

** Injection site reactions comprise application site pain, injection site discomfort, injection site pain and injection site warmth.

Paediatric patients

No adverse reactions were reported after intrathecal administration of Iomeprol both in clinical trials and in the post-marketing surveillance.

4.8.3 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 the 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 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).

Following intrathecal administration to animals, iomeprol is completely cleared from the CSF and passes into the plasma compartment.

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

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 rubber/aluminium cap.
Quantities of 20, 30, 50, 75, 100, 150, 200 or 250 ml of solution.

6.6 Special precautions for disposal and other handling

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 cannulas for piercing the stopper and drawing up the contrast medium is recommended.

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 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.

It is desirable that solutions of contrast media for intravascular and intrathecal use should be at body temperature when injected.

Any residue of contrast medium in the syringe must be discarded. Solutions not used in one examination session or waste material, such as the connecting tubes, should be disposed 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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