Proposed professional information for IMERON

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

IMERON 200 solution for injection

IMERON 250 solution for injection

IMERON 300 solution for injection

IMERON 350 solution for injection

IMERON 400 solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

IMERON 200: 1 mL contains 408 mg iomeprol, in aqueous solution equivalent to 200 mg iodine.

IMERON 250: 1 mL contains 510 mg iomeprol in aqueous solution equivalent to 250 mg iodine.

IMERON 300: 1 mL contains 612 mg iomeprol in aqueous solution equivalent to 300 mg iodine.

IMERON 350: 1 mL contains 714 mg iomeprol in aqueous solution equivalent to 350 mg iodine.

IMERON 400: 1 mL contains 816 mg iomeprol in aqueous solution equivalent to 400 mg iodine.

Table 1:

	IMERON 200	**IMERON 250**	**IMERON 300**	**IMERON 350**	**IMERON 400**
Iodine concentration (mg/mL)	200	250	300	350	400
Iodine content (g) per - 20 mL bottle	-	-	6	-	-

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- 50 mL bottle	-	12,5	15	17,5	20
- 75 mL bottle	15	-	22,5	-	-
- 100 mL bottle	-	-	30	35	40
- 150 mL bottle	30	37,5	45	52,5	-
- 200 mL bottle	-	-	60	70	80
- 500 mL bottle	-	-	-	175	200
Contrast medium concentration mg/mL	408	510	612	714	816
Contrast medium content (g) per					
- 20 mL bottle	-	-	12,24	-	-
- 50 mL bottle	-	25,5	30,6	35,7	40,8
- 75 mL bottle	30,6	-	45,9	-	-
- 100 mL bottle	-	-	61,2	71,4	81,6
- 150 mL bottle	61,2	76,5	91,8	107,1	-
- 200 mL bottle	-	102	122,4	142,8	163,2
- 500 mL bottle	-	-	-	357	408

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Osmolality at 37 °C (mosmol/kg H_2O)	362 ± 17	435 ± 20	521 ± 24	618 ± 29	726 ± 34

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear solution, practically free from visible particles in suspension.

The pH range of the aqueous solutions at shelf life is between 6,5 – 7,2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IMERON 200: Peripheral phlebography, digital subtraction phlebography, CT (brain and body), cavernosography, intravenous and intra-arterial DSA, ERCP, arthrography, hysterosalpingography, cholangiography, retrograde urethrography and retrograde pyelo-ureterography.

IMERON 250: Intravenous urography (in adults and paediatrics), peripheral phlebography, CT (brain and body), intravenous and intra-arterial DSA.

IMERON 300: Intravenous urography (in adults and paediatrics), peripheral phlebography, CT (brain and body), cavernosography, intravenous DSA, conventional angiography, intra-arterial DSA, angiocardiography (in adults and paediatrics), conventional selective coronary arteriography, interventional coronary arteriography, ERCP, arthrography, hysterosalpingography, fistulography,

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discography, galactography, cholangiography, dacryocystography, sialography, retrograde urethrography, retrograde pyelo-ureterography.

IMERON 350: Intravenous urography (in adults and paediatrics), CT (body), intravenous DSA, conventional angiography, intra-arterial DSA, angiocardiography (in adults and paediatrics), conventional selective coronary arteriography, interventional coronarography, arthrography, hysterosalpingography, fistulography, galactography, cholangiography, dacryocystography, sialography.

IMERON 400: Intravenous urography (in adults including those with renal impairment or diabetes), CT (body), conventional angiography, intra-arterial DSA, angiocardiography (in adults and paediatrics), conventional selective coronary arteriography, interventional coronary arteriography, fistulography, galactography, dacryocystography, sialography.

CT: Computed tomography.

DSA: Digital subtraction angiography.

ERCP: Endoscopic retrograde cholangio-pancreatography.

MCU: Micturating cisto-urethrography.

4.2 Posology and method of administration

General information

1. Any severe disorders of water and electrolyte balance must be corrected prior to administration. Adequate hydration must be ensured particularly in patients with multiple myeloma, diabetes mellitus, polyuria, oliguria and hyperuricaemia; also in babies, small children and the elderly.
2. Unless otherwise instructed by the doctor, a normal diet may be maintained on the day of the examination. Adequate fluid intake must be ensured. However, for two hours prior to the procedure the patient should refrain from eating.

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3. In patients with phaeochromocytoma, premedication with alpha-receptor blockers is recommended because of the risk of blood pressure crisis (see section 4.4).
4. Pronounced states of excitement, anxiety and pain can be the cause of side-effects or intensify contrast-related reactions. These patients may be given a sedative.
5. Neuroleptics and antidepressants should be discontinued 48 hours before the examination because they reduce the seizure threshold. Treatment should not be resumed until 24 hours post-procedure (see section 4.4 and 4.5). Anti-convulsant therapy must not be discontinued and should be administered in optimal dosage.

In relation to procedure

6. Non-ionic contrast media have less anti-coagulant activity *in vitro* than ionic media. Meticulous attention should therefore be paid to angiographic technique and vascular catheterisation. Non-ionic media should not be allowed to remain in contact with blood in the syringe and intra-vascular catheters should be flushed frequently to minimise the risk of clotting which, rarely, has led to serious thrombo-embolic complications after procedures.
7. Intravascular administration of contrast media should, if possible, be done with the patient lying down. The patient should be kept under observation for at least 30 minutes after the procedure.

In relation to the contrast media

8. Vials 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. The contrast medium should not be drawn into the syringe until immediately before use. Solutions not used in one examination session must be discarded.
9. When using IMERON 500 mL bottle, the contrast medium solution should be administered with an automatic injector. The tube connecting the injector to the patient (patient tube) should be replaced after each examination as it may be contaminated with blood. Unused contrast solution

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remaining in the bottle, the connection tube and the injector should be discarded at the end of the examination day. Follow the instructions given by the manufacturer of the injection system or the equipment.

10. In order to avoid possible incompatibilities, contrast media must not be mixed with other medicines.

In consideration of possible complications, the patient should be kept under observation for at least 60 minutes after the administration.

Table 2:

Indications	**Formulation mg (iodine)/mL**	**Proposed dosages**
Intravenous urography	250, 300, 350, 400	Adults: 50 – 50 mL Neonates: 3 – 4,8 mL/kg Babies: 2,5 – 4 mL/kg ≤ 1 year Children: 1 – 2,5 mL/kg ≥ 1 year
Peripheral phlebography	200, 250, 300	Adults: 10 – 100 mL, repeat if necessary[b] (10 – 50 mL upper extremities; 50 – 100 mL lower extremities)
Phlebography in DSA	200	Adults: 10 – 100 mL, repeat if necessary [b] (10 – 50 mL upper extremities; 50 – 100 mL lower extremities)
CT brain	200, 250, 300	Adults: 50 – 200 mL Children [a]
CT body	200, 250, 300, 350,	Adults: 100 – 200 mL

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	400	Children [a]
Cavernosography	200, 300	Adults: up to 100 mL
Intravenous DSA	250, 300, 350, 400	Adults: 100 – 250 mL Children [a]
Conventional angiography:		
- Arteriography of upper extremities	300, 350	Adults [b]
- Arteriography of pelvis and lower extremities	300, 350, 400	Adults [b]
- Abdominal arteriography	300, 350, 400	Adults [b]
- Arteriography of descending aorta	300, 350	Adults [b]
- Pulmonary angiography	300, 350, 400	Adults: up to 170 mL
- Cerebral angiography	300, 350	Adults: up to 100 mL
- Paediatric arteriography	300	Children: up to 130 mL [a]
- Interventional arteriography	300, 350, 400	Adults [b] Children [a]
Intra-arterial DSA		
- Cerebral	200, 300, 350	Adults: 30 - 60 ml for general view; 5 – 10 mL for selective angiography Children [a]
- Thoracic	200, 300	Adults [b]: 20 – 25 mL (aorta) repeat if necessary 20 mL (bronchial arteries)
- Aortic arch	200, 300, 350	Adults [c]
- Abdomen	200, 250, 300	Adults [c]
- Aortography	200, 300, 350	Adults [c]

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- Translumbar aortography	200, 300	Adults [b]
- Peripheral arteriography	200, 250, 300	Adults: 5 – 10 mL for selective injections up to 250 ml Children [a]
- Interventional	200, 300	Adults: 10 – 30 mL for selective injections up to 250 mL Children [a]
Angiocardiography	300, 350, 400	Adults [b] Children: 3 – 5 mL/kg
Conventional selective coronary arteriography	300, 350, 400	Adults: 4 – 10 mL per artery, repeat if necessary
ERCP	200, 300	Adults: up to 100 mL
Arthrography	200, 300, 350	Adults: up to 10 mL/injection
Hysterosalpingography	200, 300, 350	Adults: up to 35 mL
Fistulography	300, 350, 400	Adults: up to 100 mL
Discography	300	Adults: up to 4 mL
Galactography	300, 350, 400	Adults: 0,15 – 1.2 mL for injection
Dacryocystography	300, 350, 400	Adults: 2,5 – 8 mL for injection
Sialography	300, 350, 400	Adults: 1 – 3 mL for injection
Retrograde cholangiography	200, 300, 350	Adults: up to 60 mL
Retrograde urethrography	200, 300	Adults: 20 – 100 mL
Retrograde pyelo-ureterography	200, 300	Adults: 10 – 20 mL for injection

[a] = According to body weight and age.

[b] = Do not exceed 250 mL. Single injection volume depends on the vascular area to be examined.

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[c] = Do not exceed 350 mL

Method of administration:

The following methods of administration can be used: intravenous and intra-arterial.

4.3 Contraindications

Hypersensitivity to iomeprol or to any of the ingredients of IMERON (listed in section 6.1).

IMERON should be avoided in case of Waldenström's paraproteinaemia, multiple myeloma and severe liver or renal impairment.

Investigations of the female genitalia are contraindicated in suspected or confirmed pregnancy (see section 4.6) and in cases of acute inflammation.

IMERON 200: Hysterosalpingography is not to be carried out in pregnancy or in acute pelvic inflammatory conditions.

IMERON 200/250/300: Intrathecal concomitant administration of corticosteroids with contrast media, such as IMERON, is contraindicated.

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.

Fatal reactions have been associated with the administration of water-soluble contrast media.

Particular caution must be exercised in the case of hypersensitivity to iodinated contrast media.

Experience shows that patients with an allergic disposition suffer more frequently from hypersensitivity reactions. Premedication with antihistamines and/or corticoids may be considered.

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However, contrast media and prophylactic medicines should not be administered as mixed together (see section 6.2).

Treatment with medicines that lower the seizure threshold such as analgesics, antidepressants and anti-emetics of the phenothiazine class, and neuroleptics should be discontinued 48 hours before the examination. Treatment should not be resumed until 24 hours post-procedure (see section 4.5).

A positive history of allergy, asthma or untoward reactions during previous similar investigations indicates a need for extra caution since, as with other contrast media, IMERON 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 measure should be immediately available.

The primary treatments are tabulated 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	Angio-oedema Urticaria Bronchospasm Hypotension	Oxygen. IV fluids. Adrenergics. (IV epinephrine/adrenaline). Inhaled beta$_2$-adrenergics Antihistamines (H_1- and H_2- blockers) Corticosteroids.

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Hypotensive	Hypotension	IV fluids.
Vagal reaction	Hypotension Bradycardia	IV fluids. IV atropine.

In consideration of possible complications, the patient should be kept under observation for at least 60 minutes after the administration.

Elderly: There is a special risk of reactions involving the circulatory system such that myocardial ischaemia, major dysrhythmias 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 patients.
Patients using beta-adrenergic blocking medicines, 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.

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 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.

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 and these effects appear more evident in patients with latent or overt hyperthyroidism or goitre. Thyroid storms have been reported following administration of IMERON.
Use may interfere with thyroid function tests. Following administration of iodinated contrast media, the capacity of the thyroid tissue to take up radio-isotopes for the diagnosis of thyroid disorders is

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reduced for up to two weeks, or even longer in individual cases.

Renal failure: Pre-existing renal impairment may predispose to acute renal dysfunction following contrast media administration, 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 contrast media administration, preferably by maintaining IV infusion before and during the procedure and until the contrast medium has been cleared by the kidneys;
- avoiding, whenever possible, the administration of nephrotoxic medicines or major surgery or procedures such as renal angioplasty, until the contrast medium has been cleared;
- postponing a new contrast agent examination until renal function returns to pre-examination levels. Patients on dialysis may receive contrast media, such as IMERON, which may be cleared by dialysis.

Diabetes mellitus: Renal impairment may precipitate lactacidosis in diabetic patients with renal damage, treated with biguanides (metformin). To prevent onset of lactic acidosis in these patients, metformin should be stopped at the time or 48 hours prior to the administration of the contrast medium, and only re-instated after 48 hours if serum creatinine/estimated glomerular filtration rate (eGFR) is unchanged from the pre-imaging level.
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.

Patients with phaeochromocytoma may develop severe, occasionally uncontrollable hypertensive crises during intravascular administration. Premedication with an alpha-blocker is recommended in these patients before intra-arterial injection of contrast media under the supervision of a medical practitioner.

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Anxiety, pain: Pronounced excitement, anxiety and pain can cause side effects or intensify reaction to the contrast medium. A sedative may be given.

Cardiac disorders: Care should be taken in severe cardiac disease particularly heart failure and coronary artery disease. Reactions may include pulmonary oedema, haemodynamic changes, ischaemic electrocardiogram (ECG) changes and dysrhythmias.
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 catheterisation procedure are increased.

Central nervous system (CNS) disorder: Particular care should be paid to the intravascular administration of IMERON in patients with acute cerebral infarction, acute intracranial haemorrhage and conditions involving blood brain barrier (BBB) damage, brain oedema or acute demyelination.
The presence of intracranial tumours or metastases and a history of epilepsy may increase the probability of the occurrence of convulsive seizures.
Neurological symptoms related to cerebrovascular diseases, intracranial tumours/metastasis or degenerative, ischaemic or inflammatory pathologies may be exacerbated. These patients have an increased risk of transient neurological complications.

Contrast induced encephalopathy: Encephalopathy has been reported with the use of IMERON (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 IMERON, and generally resolves within days.
The product should be used with caution in patients with conditions that disrupt the integrity of the

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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 IMERON should be discontinued and appropriate medical management should be initiated.
Cerebral ischaemic phenomena may be caused by intravascular injection.
In acute and chronic alcoholism, the increase in BBB 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 reduced seizure threshold.

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

Myasthenia gravis: The administration of iodinated contrast media may worsen myasthenia signs and symptoms.

Vascular disorders: Special care is required when investigations are performed in patients with suspected thrombosis, phlebitis, severe ischaemic disease, local infection or a totally obstructed arterovenous system.

Paediatric population

Children: Infants up to 1 year, especially newborn, are particularly susceptible to electrolyte imbalances and haemodynamic alterations. Care should be taken regarding the dosage to be used. Transient thyroid suppression or hypothyroidism has been observed in children after exposure to iodinated contrast media. Following a diagnostic procedure, this has been more frequently observed in neonates and premature infants and also following procedures associated with higher doses. Neonates may also be exposed via maternal exposure. In neonates, especially preterm infants, who have been exposed to IMERON, either through the mother during pregnancy or in the neonatal

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period, it is recommended to monitor thyroid function. If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalized.

4.5 Interaction with other medicines and other forms of interaction

Use of IMERON 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 medicines should not be administered prior to IMERON.

The presence of renal damage in diabetic patients is one of the risk factors predisposing to renal impairment following contrast media administration. Renal damage may precipitate lactic acidosis patients who are taking metformin (see 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).

IMERON 200/250/300: Epidural and intrathecal corticosteroids should never be concurrently administered with IMERON®, because corticosteroids may promote and affect the signs and symptoms of arachnoiditis (see section 4.3).

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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

The safety of IMERON in human pregnancy has not been established. Therefore avoid use in pregnancy (see section 4.3). In neonates who have been exposed to IMERON *in utero*, it is recommended to monitor thyroid function (see section 4.4).

Breastfeeding

No human data exist concerning the excretion of IMERON in breast milk. Animal studies have demonstrated that the excretion of IMERON in breast milk is similar to that of other contrast agents.

As a precautionary measure, breastfeeding should be discontinued prior to the administration of IMERON and should not be recommenced until 24 hours after the administration of the contrast medium.

4.7 Effects on ability to drive and use machines

There is no known effect on the ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile

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.

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Anaphylaxis (anaphylactoid/hypersensitivity reactions) may manifest with various symptoms, and rarely does any one patient develop all the symptoms. Typically, in 1 to 15 minutes (but rarely after as long as 2 hours), the patient complains of feeling abnormal, agitation, flushing, feeling hot, sweating increased, dizziness, lacrimation increased, rhinitis, palpitations, paraesthesia, pruritus, head throbbing, pharyngolaryngeal pain and throat tightness, dysphagia, cough, sneezing, urticaria, erythema, and mild localised oedema or 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 IMERON 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 4,920 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.

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Tabulated summary of adverse reactions

The following terminologies have been used in order to classify the occurrence of adverse reactions: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to, < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1 000)**	**Frequency unknown***
Blood and lymphatic system disorders				Thrombocytopenia, haemolytic anaemia
Immune system disorders			Anaphylactoid reaction (characterised by cardiovascular, respiratory and cutaneous symptoms)	
Psychiatric disorders		Agitation		Anxiety.
Nervous system disorders	Headache	Dizziness, paralysis	Tremor, confusion, loss	Transient ischaemic attack, dysarthria,

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System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1 000)**	**Frequency unknown***
			of consciousness, visual field defect, syncope, aphasia, convulsions and coma	paraesthesia, cerebral oedema, amnesia, meningitis, somnolence, taste abnormality, hypoxic encephalopathy, contrast induced encephalopathy***
Eye disorders				Blindness transient, visual disturbance, conjunctivitis, lacrimation increased, photopsia, photophobia
Cardiac disorders		Bradycardia, tachycardia, extrasystoles	Cyanosis	Cardiac arrest, myocardial infarction, cardiac failure, angina pectoris, pulmonary oedema, dysrhythmias,

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System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1 000)**	**Frequency unknown***
				ventricular or atrial fibrillation, atrioventricular block.
Vascular disorders	Pallor	Hypertension, hypotension	Vasodilatation, circulatory collapse	Circulatory collapse or shock, flushing, pallor
Respiratory, thoracic and mediastinal disorders		Dyspnoea, nasal congestion, laryngeal oedema		Respiratory arrest, acute respiratory distress syndrome (ARDS), pulmonary oedema, pharyngeal/laryngeal oedema, bronchospasm, asthma, stridor, cough, sneezing, pharynx discomfort, laryngeal spasm or discomfort, rhinitis, hypoxia, dysphonia

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System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1 000)**	**Frequency unknown***
Gastrointestinal disorders	Nausea	Vomiting		Acute pancreatitis, diarrhoea, abdominal pain, salivary hypersecretion, dysphagia, ileus, salivary gland enlargement
Skin and subcutaneous tissue disorders		Rash, erythema, wheals, urticaria, pruritus, sweating increased		Acute generalized exanthematous pustulosis, angioedema, pruritis, urticaria, rash, erythema, dermatitis, eczema, sweating increased
Musculoskeletal and connective tissue disorder		Back pain	Muscle spasm	Arthralgia, muscle weakness
Renal and urinary disorders			Renal failure, oliguria,	Acute kidney injury

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System Organ Class	**Adverse Reactions**			
	Clinical Trials			**Post-marketing Surveillance**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1 000)**	**Frequency unknown***
			proteinuria.	
General disorders and administration site conditions	Feeling hot, injection site warmth and pain	Chest pain, injection site haemorrhage, rigors, injection site haemorrhage, pyrexia	Asthenia	Oedema, chills, fever, injection site reaction**, coldness local, malaise, Thirst
Investigations			Blood creatinine increased	Abnormal electrocardiogram, abnormal liver function tests

* 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.

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*** 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.

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 population

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

The safety profile of IMERON is similar in children and adults.

Transient hypothyroidism may occur in neonates when exposed to IMERON, especially in preterm or low birth weight neonates.

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

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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 IMERON is important. It allows continued monitoring of the benefit/risk balance of IMERON. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.28 Contrast media

Pharmacotherapeutic group: Water-soluble, nephrotropic, low osmolar X-ray contrast media

ATC code: V08AB10

Iomeprol, N,N’-bis(2,3-dihydroxypropyl)-5[(hydroxyacetyl)methylamino]-2,4,6-triiodo-1,3-benzenedicarboxamide, 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

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400 mg iodine per mL. Even at this concentration the low viscosity allows delivery of high doses through thin catheters.

The physicochemical characteristics of injectable solutions of IMERON are included in table below:

Iodine	**Osmolality***	**Viscosity**	
Concentration *mg/mL*	*mosmol/kg water*	*mPa.s*	
	$(x \pm s \cdot t_{95})$	$(x \pm s \cdot t_{95})$	
	37 ºC	**20 ºC**	**37 ºC**
150	301 ± 14	2,0 ± 0,2	1,4 ± 0,1
200	362 ± 17	3,1 ± 0,2	2,0 ± 0,2
250	435 ± 20	4,9 ± 0,4	2,9 ± 0,3
300	521 ± 24	8,1 ± 0,7	4,5 ± 0,4
350	618 ± 29	14,5 ± 1,1	7,5 ± 0,6
400	726 ± 34	27,5 ± 2,3	12,6 ± 1,1

5.2 Pharmacokinetic properties

The pharmacokinetics of iomeprol following intravascular administration when described by a two-compartment model, show a rapid phase for drug distribution and a slower phase for medicine elimination. In 18 healthy volunteers the mean half-lives of the distribution and elimination phases were 23 ± 14 (s) min and 109 ± 20 (s) min, respectively, with an excretion of 50 % by the urinary tract within 2 hours after administration.

Distribution volume is similar to that of extracellular fluid. There is no significant serum protein binding and iomeprol is not metabolised.

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

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within 2 hours).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol

Hydrochloric acid (pH adjustment)

Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, IMERON must not be mixed with other medicines.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Not intended for the withdrawal of multiple doses. Any portion of the solution not used in one examination session must be discarded.

Unused contrast solution remaining in the IMERON 400, 500 mL bottle, the connection tubes and the injector should be discarded at the end of the examination day, following the instructions given by the manufacturer of the injection system or the equipment.

Store at or below 25 ºC.

Protect from light and secondary X-rays.

6.5 Nature and contents of container

Clear colourless glass containers (vials/bottles) with closures made of elastomeric material (chlorobutyl rubber or bromobutyl rubber) and flip-off caps composed of an aluminium ring with a central hole through which a polypropylene disc is inserted which may be available in different

colours.

Pack size:

IMERON 200: 75 mL and 150 mL bottles.

IMERON 250: 50 mL and 150 mL bottles.

IMERON 300: 20 mL, 50 mL, 75 mL, 100 mL, 150 mL and 200 mL bottles.

IMERON 350: 50 mL, 100 mL, 150 mL and 200 mL and 500 mL bottles.

IMERON 400: 50 mL, 100 mL, 200 mL and 500 mL bottles.

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 discoloured or particulate matter is present.
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 products.

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.

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7. HOLDER OF CERTIFICATE OF REGISTRATION

Axim Pharmaceuticals (Pty) Ltd

63 Old Pretoria Main Road

Halfway House 1685

Midrand, South Africa

8. REGISTRATION NUMBERS

IMERON 200: 32/28/0714

IMERON 250: 32/28/0715

IMERON 300: 32/28/0716

IMERON 350: 32/28/0717

IMERON 400: 32/28/0718

9. DATE OF FIRST AUTHORISATION

3 April 2000

10. DATE OF REVISION OF THE TEXT

To be allocated.

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