Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Imagopaque 300 mg I/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	Strength	Content per. ml.
Iopentol (INN)	300 mg I/ml	658 mg equiv. 300 mg I

Iopentol is a non-ionic, monomeric, triiodinated, water-soluble X-ray contrast medium.

The osmolality and viscosity values of Imagopaque are as follows:

Concentration	Osmolality* Osm/kg H_2O	Viscosity (mPa s)	
	37ºC	20ºC	37ºC
300 mg I/ml	0.64	13.2	6.5

* Method: Vapour – pressure osmometry.

3 PHARMACEUTICAL FORM

Solution for injection. Imagopaque injection is a clear colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

X-ray contrast medium for arteriography, urography, phlebography and CT-enhancement, arthrography, endoscopic retrograde cholangiopancreatography (ERCP), hysterosalpingography, gastrointestinal studies using oral water-soluble contrast medium.

4.2 Posology and method of adminstration

The dosage depends on the type of examination, the condition of the patient and the technique used. Usually the same iodine concentration and volume is used as for other iodinated X-ray contrast media in current use. Adequate hydration should be assured before and after administration as for other contrast media.
For intravenous and intra-arterial use, and use in body cavities.

The following dosages may serve as a guide:

Guidelines for Intravenous use

Indication	Concentration	Volume	Comments
Urography			
Adults	300 mg I/ml or 350 mg I/ml	40-80 ml	In high-dose urography higher doses can be used.
children < 1 year	300 mg I/ml	3 ml/kg	
children > 1 year	300 mg I/ml or 350 mg I/ml	1.5-2 ml/kg 1-2 ml/kg (max. 60 ml)	
Phlebography (leg)	200 mg I/ml 250 mg I/ml or 300 mg I/ml	20-100 ml/leg	
CT-enhancement			
Adults	300 mg I/ml or 350 mg I/ml	50-150 ml	Total amount of iodine usually 20-60 g
children < 2 years	300 mg I/ml	> 2.5 ml/kg	Total amount of iodine usually 10-30 g
children > 2 years	300 mg I/ml	1-2.5 ml/kg	

Guidelines for Intra-arterial use

Indication	Concentration	Volume	Comments
Arteriographies			
arch aortography select.	300 mg I/ml	30-40 ml/inj	
cerebral aortography	300 mg I/ml	5-10 ml/inj	
femoral	300 mg I/ml	40-60 ml/inj	
	150 mg I/ml or 300 mg I/ml	30-50 ml/inj	
Cardioangiography			
Adults:			
Left ventricle and aortic root inj	350 mg I/ml	30-60 ml/inj	
select coronary	350 mg I/ml	4-8 ml/inj	
children:	300 mg I/ml or 350 mg I/ml	depending on age, weight, and pathology (max 8 ml/kg)	

Guidelines for Body Cavities

Indication	Concentration	Volume	Comments
Arthrography	300 mg I/ml or 350 mg I/ml	10-20 ml 5-10 ml	
ERCP	150 mg I/ml 200 mg I/ml or 250 mg I/ml	20-50 ml	
Gastrointestinal studies – oral use	300 mg I/ml or 350 mg I/ml	10-200 ml	Depending on kind of examination
Hysterosalpingography	250 mg I/ml	10-50 ml	

4.3 Contraindications

Manifest thyrotoxicosis. History of serious reaction to Imagopaque.

4.4 Special warnings and precautions for use

Special precautions for use of non-ionic monomeric contrast media in general:
A positive history of **allergy, asthma** or untoward **reactions** to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H_1 and H_2 antagonists might be considered in these cases.

The risk of serious reactions in connection with use of Imagopaque is regarded as minor. However, iodinated contrast media may provoke **anaphylactoid** reactions or other manifestations of **hypersensitivity**. A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment, should a serious reaction occur. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.

Non-ionic contrast media have less effect on the coagulation system *in vitro*, compared to ionic contrast media. When performing vascular catheterization procedures one should pay meticulous attention to the angiographic technique and flush the catheter frequently (e.g.: with heparinized saline) so as to minimize the risk of *procedure related* thrombosis and embolism.

Adequate **hydration** should be assured before and after contrast media administration. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction, as well as to infants, small children and elderly patients. Young **infants** (age < 1 year) and especially **neonates** are susceptible to electrolyte disturbance and haemodynamic alterations.

Care should also be taken in patients with **serious cardiac disease** and **pulmonary hypertension** as they may develop haemodynamic changes or arrhythmias.

Patients with **acute cerebral pathology**, tumours or a history of **epilepsy** are predisposed for seizures and merit particular care. Also **alcoholics** and **drug addicts** have an increased risk for seizures and neurological reactions.

To prevent acute renal failure following contrast media administration, special care should be exercised in patients with pre-existing **renal impairment** and **diabetes mellitus** as they are at risk. Patients with **paraproteinemias** (myelomatosis and Waldenström's macroglobulinemia) are also at risk.

Preventive measures include:

- Identification of high risk patients
- Ensuring adequate hydration. If necessary by maintaining an i.v. infusion from before the procedure until the contrast medium has been cleared by the kidneys.
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, or major surgery, until the contrast medium has been cleared.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

To prevent lactic acidosis, serum creatinine level should be measured in diabetic patients treated with **metformin** prior to intravascular administration of iodinated contrast medium.
Normal creatinine: Administration of metformin should be stopped at the time of administration of contrast medium and not resumed for 48 hours or until renal function is normal.
Abnormal renal function: Metformin should be stopped and the contrast medium examination delayed for 48 hours. Metformin should only be restarted if renal function is unchanged.
In emergency cases where renal function is abnormal or unknown, the physician should weight the risk/benefit of the contrast medium examination, and precautions should be implemented: Metformin stopped, hydration, monitoring of renal function and signs of lactic acidosis.

Particular care is required in patients with severe disturbance of both renal and hepatic function as they may have significantly delayed contrast medium clearance. Patients on **haemodialysis** may receive contrast media for radiological procedures provided dialysis is performed immediately afterwards.

The administration of iodinated contrast media may aggravate the symptoms of **myasthenia gravis**. In patients with **phaeochromocytoma** undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis. Special care should be exercised in patients with **hyperthyroidism**. Patients with multinodular **goiter** may be at risk of developing hyperthyroidism following injection of iodinated contrast media. One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media.

Extravasation of contrast media occurs rarely and gives rise to local pain and oedema, which usually recedes without sequela. However, inflammation and even tissue necrosis have been seen. Elevating and cooling the affected site is recommended as routine measures. Surgical decompression may be necessary in cases of compartment syndrome.

Observation time:
After contrast medium administration the patient should be observed for at least 30 minutes, since the majority of serious side effects occur within this time. However, experience shows that hypersensitivity reactions may appear up to several hours or days post injection.

4.5 Interaction with other medicinal products and other forms of interaction

Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking **metformin** (see section 4.4 Special warnings and special precautions for use).

Patients treated with **interleukin-2** less than two weeks previously have been associated with an increased risk for delayed reactions (flu-like symptoms or skin reactions).

All iodinated contrast media may interfere with tests on thyroid function, thus the iodine binding capacity of the thyroid may be reduced for up to several weeks.

High concentrations of contrast media in serum and urine can interfere with **laboratory tests** for bilirubin, proteins of inorganic substances (e.g. iron, copper, calcium and phosphate). These substances should therefore not be assayed on the day of examination.

4.6 Pregnancy and lactation

Although animal studies have revealed no impaired fertility or teratogenicity due to iopentol, its use during pregnancy

should be restricted to a minimum. The highest risk associated with use during pregnancy is from the X-rays and not the contrast medium. The product should not be used in pregnancy unless benefit outweighs risk and it is considered essential by the physician.

The degree of excretion into human milk is not known, although expected to be low. Breast feeding should be discontinued prior to administration of Imagopaque and should not be recommenced until at least 24 hours after.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

General (applies to all uses of iodinated contrast media):
Below are listed possible side effects in relation with radiographic procedures which include the use of Imagopaque. For side effects specific to mode of administration, please refer to these specific sections.

Undesirable effects associated with the use of iodinated contrast media are usually mild to moderate and transient in nature, and less frequent with non-ionic than with ionic contrast media. Serious reactions as well as fatalities are only seen on very rare occasions.
The most frequently adverse event is a **mild, general sensation** such as a feeling of warmth or a transient metallic taste.

Gastrointestinal reactions like nausea or vomiting are rare (incidence <1:100, but >1:1000) and abdominal discomfort/pain is very rare (incidence <1:1000).

Other reactions such as headache or dizziness, paraesthesia, shivering, palpitation, visual disorders and hypertension are very rare.

Hypersensitivity reactions are rare and usually present as mild respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus and angioedema. They may appear either immediately after the injection or up to a few days later. Severe till toxic skin reactions have been reported. Hypotension or fever may occur. Severe manifestations such as laryngeal oedema, bronchospasm or pulmonary oedema are very rare.

Anaphylactoid reactions may occur irrespectively of the dose and mode of administration and mild symptoms of hypersensitivity may represent the first signs of a serious reaction. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the vascular access. In patients using beta blockers the bradycardia may not respond to shock and thereby these patients present with atypical symptoms of anaphylaxis which may be misinterpreted as a vagal reaction.

Vagal reactions giving hypotension and bradycardia are seen on very rare occasions.

Intravascular use (Intraarterial and Intravenous use):
Please first read the section labelled "General". Below, only undesirable events with frequency during intraarterial use of Imagopaque are described.

The nature of the undesirable effects specifically seen during intraarterial use depend on the site on injection and dose given. Selective arteriographies and other procedures in which the contrast medium reaches a particular organ in high concentrations may be accompanied by complications in that particular organ.

Distal **pain or heat sensation** in peripheral angiography is common (incidence >1:10).

A transient increase in S-creatinine is common after iodinated contrast media, but usually of no clinical relevance. Renal failure is very rare. However, renal failure may occur in high risk patients and among such patients fatalities have been reported.

Arterial spasms may follow injection into coronary, cerebral or renal arteries and result in transient ischaemia.

Neurological reactions are very rare. They may include seizures or transient motor or sensory disturbances. On very rare occasions the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex being visible on CT-scanning until the day following examination, sometimes associated with transient confusion or cortical blindness.

Cardiac complications are very rare, including arrhythmias, depression or signs of ischaemia. Hypertension may occur.

Post phlebographic thrombophlebitis or thrombosis is very rare.

Use in Body Cavities
Please first read the section labelled "General". Below, only undesirable events with frequency during use of Imagopaque in body cavities are described.

Systemic hypersensitivity reactions are rare.

Endoscopic Retrograde Cholangio Pancreatography (ERCP): Some elevation of amylase levels is common. Post ERCP renal opacification is seen on rare occasions and is associated with an increased risk of post ERCP pancreatitis. Rare cases of necrotizing pancreatitis have also been described.

Oral use: Gastrointestinal upset occasionally occurs.

Hysterosalpingography (HSG): Transient and **mild pain** in the lower abdomen is common.

Arthrography: Post procedural pain is common. Frank arthritis is rare. The possibility of infective arthritis should be considered in such cases.

4.9 Overdose

Preclinical data indicate a high safety margin for Imagopaque and no fixed upper dose level has been established for routine intravascular use. Symptomatic overdosing is unlikely in patients with a normal renal function. The duration of the procedure is important for the renal tolerability of high doses of contrast media (t½ ~ 2 hours). Accidental overdosing is most likely following complex angiographic procedures in children, particularly when multiple injections of contrast media with high concentration are given.

In cases of overdose, any resulting water- or electrolyte imbalance must be corrected. Renal function should be monitored for the next 3 days. If needed, haemodialysis may be used for clearance of excessive contrast medium. There is no specific antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iopentol in healthy volunteers, no significant deviation from preinjection values has been found. The few changes observed in the laboratory parameters were minor and considered to be of no clinical importance

5.2 Pharmacokinetic properties

Close to 100 per cent of the intravenously injected iopentol is excreted unchanged through the kidneys within 24 hours in patients with normal renal function. The maximum urinary concentration of iopentol appears within approximately 1 hour after injection. No metabolites have been detected. The protein binding is low (less than 3%).

5.3 Preclinical safety data

IMAGOPAQUE® has a very low acute intravenous toxicity in mice and rats with LD - 50 values similar to those of other non-ionic monomeric contrast media.

Excretion studies in rats and pigs have shown that iopentol is mainly excreted in the urine, and to a minor extent in the faeces (rats: 12%, pigs: 2.5%, of dose).

No specific organ enrichment of iopentol has been found, and no metabolites have been detected.

Renal studies in rats and rabbits showed iopentol to be at least as well tolerated as other non-ionic contrast media, including iohexol, and much better than the ionic monomers.

Testing of the effect of iopentol on haemodynamic and biochemical- pharmacological parameters in dogs and rabbits further demonstrated the good tolerability of iopentol.

Local tolerability of iopentol expressed as degree of endothelial injury to rabbit aorta, has been found superior to conventional ionic media.

Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or teratogenicity due to iopentol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The following excipients are included:

Trometamol
Sodium calcium edetate
Hydrochloric acid (pH adjustment)
Water for injections

6.2 Incompatibilities

No incompatibility has been found. However, other drugs should not be directly mixed with Imagopaque. A separate syringe and needle should be used.

6.3 Shelf Life

The shelf-life is 3 years for Imagopaque injection.

6.4 Special precautions for storage

Imagopaque should be stored between 2°C - 30°C and protected from light. The product in polypropylene bottles may be stored at 37°C for up to 1 month prior to administration, protected from light. Any unused portions must be discarded.

The product should be kept in the box until just before use.

6.5 Nature and contents of container

The product is filled into polypropylene bottles. The bottles are closed with chlorobutyl rubber stoppers (Ph. Eur. Type I), and supplied with a plastic screw cap which is provided with a tamper proof ring.

The product is supplied as:
1 polypropylene bottle of 75 ml
10 polypropylene bottles of 75 ml
1 polypropylene bottle of 100 ml
10 polypropylene bottles of 100 ml
1 polypropylene bottle of 150 ml
10 polypropylene bottles of 150 ml
1 polypropylene bottle of 175 ml
10 polypropylene bottles of 175 ml
1 polypropylene bottle of 200 ml
10 polypropylene bottles of 200 ml

6.6 Instructions for use and handling

Like all parenteral products, Imagopaque should be inspected visually for particulate matter, discolouration and the integrity of the container prior to use. The product should be drawn directly into the syringe immediately before use. The bottles are intended for single use only, any unused portions must be discarded.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 735/7/14

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