Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Optiray 300 mg I/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 636 mg ioversol equivalent to 300 mg Iodine

Osmolality: 645 mosmoles/kg
Viscosity: 8.2 mPa · s (at 25°C)
Viscosity: 5.5 mPa · s (at 37°C)
Contains Iodine per ml: 300 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion. Clear, colourless to faint yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.
Optiray 300 is a non-ionic X-ray contrast medium that is indicated in adults for use in cerebral, peripheral, visceral, and renal arteriography, venography, intravenous urography and in intraarterial and intravenous digital subtraction angiography (IA-DSA). Optiray 300 is also indicated in adults for use in computed tomography (CT) of the head and body. Optiray 300 may also be used in children for cerebral, peripheral and visceral arteriography and for intravenous urography.

4.2 Posology and method of administration

Adults
Recommended dosage schedule:

Procedure	Dosage *	Maximum Total Dose
Cerebral Arteriography		
- Carotid or vertebral artery	2-12 ml	200 ml
- Aortic arch	20-50 ml	200 ml
Peripheral Arteriography	10-90 ml	250 ml
Venography	50-100 ml	250 ml
Visceral Arteriography	12-60 ml	250 ml
Renal Arteriography	6-15 ml	250 ml
Intravenous Urography	50-75 ml	150 ml
Head Computed Tomography	50-150 ml	150 ml
Body Computed Tomography	25-150 ml	150 ml
Intraarterial Digital Subtraction Angiography	5-80 ml	250 ml
Intravenous Digital Subtraction Angiography	30-50 ml	250 ml

* Repeated as necessary

Elderly
Dosage as for adults. Where poor demonstration is to be expected, the dosage can be increased to the maximum.

Paediatric population
Recommended dosage schedule:

Procedure	Dosage *	Maximum Total Dose
Cerebral Arteriography	1-3 ml/kg	100 ml

Peripheral Arteriography	1-3 ml/kg	100 ml
Visceral Arteriography	1-3 ml/kg	100 ml
Intravenous Urography	2 ml/kg (> 1 year of age)	100 ml
	3 ml/kg (< 1 year of age)	not known

Safety and efficacy of Optiray 300 in children in any other indication have not yet been established.

It is recommended that intravascularly administered iodinated contrast agents are warmed up to body temperature prior to injection. As with all radiopaque contrast agents, the lowest dose necessary to obtain adequate visualisation should be used.

Appropriate resuscitation equipment should be available.

4.3 Contraindications

- Hypersensitivity to iodine-containing contrast media, the active substance, or to any of the excipients listed in section 6.1.
- Manifest hyperthyroidism.

4.4 Special warnings and precautions for use

Serious or fatal reactions have been associated with the administration of iodinated X-ray contrast media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

Procedures should be performed under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognising and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, the patient should be observed and emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

As with all other X-ray contrast media, Optiray may cause anaphylaxis or other manifestations of pseudo-allergic intolerance reactions, e.g. nausea, vomiting, dyspnoea, erythema, urticaria and hypotension. A higher incidence of such reactions has been observed in patients with a history of asthma or of previous intolerance reactions to other contrast media, or any history of allergy or hypersensitivity. In such patients, the benefit should clearly outweigh the risks (see section 4.3 Contraindications).

Severe, life-threatening, systemic hypersensitivity reactions such as drug reaction/rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients administered Optiray. Early or late manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately.

The occurrence of severe idiosyncratic reactions has prompted the use of several pre-testing methods. However, pre-testing cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pre-testing in predicting potential adverse reactions.

A positive history of allergies does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised (see section 4.3 Contraindications). Appropriate resuscitation measures should be immediately available.

Pre-medication with antihistamines and corticosteroids to avoid or minimise allergic reactions should be considered. Reports indicate that such pre-treatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

The patient should also be informed that allergic reactions may develop up to several days post administration; in such case, a physician should be consulted immediately.

General anaesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anaesthesia.

In angiographic procedures, the possibility of dislodging plaque or damaging or perforating the vessel wall should be considered during catheter manipulation and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Angiography should be avoided whenever possible in patients with homocystinuria due to an increased risk of thrombosis and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed haemodynamic disturbances, which may be associated with a transitory increase in the circulating osmotic load.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that the additional risk be evaluated in such patients before use of any contrast medium (see section 4.3 Contraindications).

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, diabetes mellitus, homozygous sickle cell disease, multiple myeloma or other paraproteinaemia, anuria, particularly when large doses are administered. Serious renal effects, including acute renal failure, may occur in these patients. Although neither the contrast agent nor dehydration has been proved separately to be the cause of renal failure, it has been speculated that the combination of both may be causative. The risk in patients with impaired renal function is not a contraindication to the procedure: however, special precautions, including maintenance of normal hydration and close monitoring, are required.

An effective hydration prior to the administration of Optiray is essential and may decrease the risk of renal injury. Preparatory dehydration is dangerous and may contribute to acute renal failure.

Administration of radiopaque materials to patients known or suspected of having phaeochromocytoma should be performed with caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedure may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. Premedication with α- and ß-blockers is advisable when the contrast medium is administered intravascularly due to the risk of a hypertensive crisis. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

In patients with homozygous sickle cell disease, hyperosmolar agents such as X-ray contrast media may effect sickling of erythrocytes. Hence, there is a need for careful consideration before the intra-arterial administration of such agents to patients with homozygous sickle cell disease.

The anticoagulant effect of non-ionic X-ray contrast media has been shown, in vitro, to be less than that of conventional ionic agents at comparable concentrations. Similar results were found in some in vivo studies. For this reason, meticulous angiographic techniques are recommended, e.g. frequent flushing of standard angiographic catheters and avoiding prolonged contact of blood with the contrast agent in syringes and catheters.

Serious neurologic events have been observed following direct injection into cerebral arteries or vessels supplying the spinal cord or in angiocardiography, due to inadvertent filling of the carotids. A cause-effect relationship to the contrast medium has not been established, since the patient's pre-existing condition and procedural techniques could be causative factors in themselves.

Optiray should be injected with caution to avoid perivascular application. This is especially important in patients with severe arterial or venous disease. However, significant extravasation of Optiray may occur especially during the use of power injectors. Generally, it is tolerated without substantial tissue injury applying conservative treatment. However, serious tissue damage (e.g. ulceration) has been reported in isolated cases requiring surgical treatment.

Paediatric population

In neonates and particularly in premature neonates, it is recommended to control TSH level and T4, 7-10 days and 1 month after the administration of iodinated contrast media because of the risk of hypothyroidism due to iodine overload.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

The following interactions have been reported after the administration of other iodinated contrast media. They are generally accepted as being attributable to this class of contrast media.

Renal toxicity has been reported in small numbers of patients with liver dysfunction, who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular X-ray contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.

Lactic acidosis has been reported in patients with reduced renal function receiving Metformin at the time of an X-ray examination involving parenteral administration of iodinated contrast media. Depending on the level of renal impairment, Metformin should therefore be considered to be stopped in diabetic patients between 48 hours before and at the time of the examination. The use of Metformin should not be resumed for 48 hours, and should only be restarted if renal function/serum creatinine remains within the normal range or has returned to baseline.

Iodinated X-ray contrast media may reduce the capacity of the uptake of iodine by the thyroid gland. For this reason the results of PBI (protein-bound iodine) and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated X-ray 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.

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.
There are, however, no adequate and well controlled studies in pregnant women.
It is not known whether ioversol crosses the placental barrier or reaches foetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter foetal tissue passively.
Because animal teratology studies are not always predictive of human response, caution should be exercised when prescribing to pregnant women. Since any X-ray investigation during pregnancy may involve a potential risk, the risk/benefit ratio should be carefully weighed. If a better and safer alternative is available, an X-ray investigation involving X-ray contrast media should be avoided.

Breast-feeding
It is not known whether Ioversol is excreted in human milk. However, many injectable X-ray contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in breastfed infants, caution should be exercised when intravascular contrast media are administered to breastfeeding women because of potential adverse reactions, and consideration should be given to temporarily discontinuing breastfeeding.

Fertility
Animal studies did not indicate direct or indirect harmful effects with respect to fertility in humans. There are, however, no adequate and well controlled clinical studies on fertility.

4.7 Effects on ability to drive and use machines

There is no known effect on the ability to drive and operate machines. However, because of the risk of early reactions driving or operating machinery is not advisable for 1 hour following the time of injection.

4.8 Undesirable effects

Frequencies for adverse drug reactions are defined as follows:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10,000 to <1/1000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

a. Summary of the safety profile

Adverse reactions following the use of Optiray formulations are generally independent of the dose administered. Usually, they are mild to moderate, of short duration and resolve spontaneously (without treatment). However, even mild adverse reactions may be the first indication of a serious, generalized reaction that can occur rarely after iodinated contrast media. Such serious reactions may be life-threatening and fatal, and usually affect the cardiovascular system. Most adverse drug reactions to Optiray formulations occur within minutes after administration, however contrast related hypersensitivity reactions may occur with a delay of some hours up to several days.

b. Tabulated summary of adverse reactions

From clinical studies, mild discomfort, including sensation of heat or cold, pain during the injection, and/or transient taste perversion, was noted in 10% to 50% of patients. In a large post-marketing study, other side effects occurred in a total of 1.1% of the patients; the most frequent were nausea (0.4%), skin reactions such as urticaria or erythema (0.3%), and vomiting (0.1%). All other events occurred in less than 0.1% of the patients.

Immune system disorders:	
Very rare	anaphylactoid (hypersensitivity) reaction
Not known	anaphylactic shock

Endocrine disorders:	
Not known	transient neonatal hypothyroidism

Psychiatric disorders:	
Very rare	confusional state; agitation; anxiety

Nervous system disorders:	
Rare	syncope; tremor; vertigo (including dizziness, light-headedness); headache; paraesthesia; dysgeusia
Very rare	loss of consciousness; paralysis; speech disorders; somnolence; stupor; aphasia; dysphasia; hypoaesthesia
Not known	convulsions; dyskinesia; amnesia

Eye disorders:	
Rare	vision blurred
Very rare	conjunctivitis allergic (including eye irritation, ocular hyperaemia, watery eyes, swelling of conjunctiva, etc.)
Not known	blindness transient

Ear and labyrinth disorders:	
Very rare	tinnitus

Cardiac disorders:	
Rare	tachycardia
Very rare	heart block; arrhythmia; angina; ECG abnormal; bradycardia; atrial fibrillation

Not known	cardiac arrest; ventricular fibrillation; coronary artery spasm; cyanosis; extrasystole; palpitations

Vascular disorders:	
Rare	hypotension; flushing
Very rare	cerebrovascular disorder; phlebitis; hypertension; vasodilation
Unknown	Shock; thrombosis; vasospasm

Respiratory, thoracic and mediastinal disorders:	
Rare	laryngeal spasm, oedema and obstruction (incl. throat tightness, stridor, etc.); dyspnoea; rhinitis (incl. sneezing, nasal congestion); throat irritation; cough
Very rare	pulmonary oedema; pharyngitis; hypoxia
Not known	respiratory arrest; asthma; bronchospasm; dysphonia

Gastrointestinal disorders:	
Uncommon	nausea
Rare	vomiting; dry mouth
Very rare	sialoadenitis; abdominal pain; tongue oedema; dysphagia; hypersalivation
Not known	diarrhoea

Skin and subcutaneous tissue disorders:	
Uncommon	urticaria
Rare	erythema; pruritus; rash
Very rare	angioedema; hyperhidrosis (incl. cold sweat)
Not known	toxic epidermal necrolysis; drug reaction with eosinophilia and systemic symptoms (DRESS); acute generalized erythematous pustulosis; erythema multiforme, pallor

Musculoskeletal, connective tissue and bone disorders:	
Very rare	muscle cramps

Renal and urinary disorders:	
Rare	micturition urgency
Very rare	acute renal failure; abnormal renal function; incontinence; haematuria; decreased creatinine clearance; BUN (blood urea nitrogen) increased
Not known	anuria; dysuria

General disorders and administration site conditions:	
Very common	feeling hot
Common	pain
Rare	face oedema (incl. eye swelling, periorbital oedema, etc.); pharyngeal oedema; chills (incl. shaking chills, feeling cold)
Very rare	oedema; injection site reactions (incl. pain, erythema, and haemorrhage up to necrosis especially after extravasation); chest pain; asthenic conditions (incl. malaise, tiredness, sluggishness, etc.); feeling abnormal
Not known	pyrexia

c. Description of selected adverse reactions

Adverse reactions may be classified as follows:

a.	Hypersensitivity or anaphylactoid reactions are mostly mild to moderate with symptoms like rash, pruritus, urticaria and rhinitis. However, serious reactions may occur. Serious anaphylactic reactions generally affect the cardiovascular and respiratory

	system. These may be life-threatening and include anaphylactic shock, cardiac and respiratory arrest, or pulmonary oedema. Fatal cases were reported. Patients with a history of allergic reactions are at increased risk of developing a hypersensitivity reaction. Other type 1 (immediate) reactions include symptoms like nausea and vomiting, skin rashes, dyspnoea, rhinitis, paraesthesia or hypotension.
b.	Vasovagal reactions e.g. dizziness or syncope which may be caused either by the contrast medium, or by the procedure.
c.	Cardiologic side effects during cardiac catheterisation e.g. angina pectoris, ECG changes, cardiac arrhythmias, conductivity disorders, as well as coronary spasm and thrombosis. Such reactions are very rare and may be caused by the contrast medium or by the procedure.
d.	Nephrotoxic reactions in patients with pre-existing renal damage or renal vasopathy, e.g. decrease in renal function with creatinine elevation. These adverse effects are transient in the majority of cases. In single cases, acute renal failure has been observed.
e.	Neurotoxic reactions after intra-arterial injection of the contrast medium e.g. visual disorders, disorientation, paralysis, convulsions, or fits. These symptoms are generally transient and abate spontaneously within several hours or days. Patients with pre-existing damage of the blood-brain barrier are at increased risk of developing neurotoxic reactions.
f.	Local reactions at the injection site may occur in very rare cases and include rashes, swelling, inflammation and oedema. Such reactions occur probably in most cases due to extravasation of the contrast agent. Extended paravasation may necessitate surgical treatment.
g.	Extravasation can cause serious tissue reactions including blistering and skin exfoliation, the extent of which is dependent on the amount and strength of the contrast solution in the tissues.

d. Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. Transient hypothyroidism was observed in neonates following the administration of iodinated radiopaque agents.

Reporting of suspected adverse reactions

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 HPRA Pharmacovigilance,

Website: www.hpra.ie

4.9 Overdose

As with all iodinated X-ray contrast media, overdoses of Optiray are potentially fatal and may affect the respiratory and cardiovascular system. Treatment should be symptomatic. Dialysis can be used to remove Optiray from the blood.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Watersoluble, nephrotropic, low osmolar X-ray contrast media
ATC code: V08AB07
Optiray 300 is a non-ionic X-ray contrast medium. Intravascular injection of Optiray opacifies those vessels in the path of the flow of the contrast medium, permitting radiographic visualisation of the internal structures until significant haemodilution occurs.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of Optiray, together with its hydrophilic properties and a very low level of binding to serum and plasma proteins, indicate that Optiray is distributed within the extracellular fluid space and eliminated quickly through the

kidneys by glomerular filtration. The mean (± se) half-lives after doses of 50 ml and 150 ml were 113 ± 8.4 and 104 ± 15 minutes respectively. Elimination via the faeces is negligible. No significant metabolism, deiodination, or biotransformation of Optiray has been observed.

5.3 Preclinical safety data

There were no findings in the preclinical testing of Optiray which could be of relevance for the prescriber in recognising the safety of this product used for the authorised indications, and which are not already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Trometamol hydrochloride
Sodium calcium edetate
Water for injections
Sodium hydroxide and/or hydrochloric acid (for pH: 6.0 to 7.4)

6.2 Incompatibilities

No other medicinal product should be mixed with Optiray.

6.3 Shelf life

3 years.
Chemical and physical in-use stability has been demonstrated for 24 hours up to 37ºC.
After use, discard the remaining solution.

6.4 Special precautions for storage

Keep the container in the outer carton in order to protect from light. Protect from X-rays. Do not store above 30°C. Optiray can be stored for one month at 37°C in a contrast medium warmer with circulating air. Do not freeze. Discard the solution in case of discolouration or particulate matter.

6.5 Nature and contents of container

Uncoloured vials and bottles composed of type I Ph. Eur. glass. Vials are fitted with 20 mm latex-free bromobutyl rubber closures and aluminium cap seals. Bottles are fitted with 32 mm latex-free bromobutyl rubber closures and aluminium cap seals.

Pack sizes:
10 x 10 ml vial.
10 x 20 ml vial.
10 x 50 ml bottle.
10 x 75 ml bottle.
10 x 100 ml bottle.
10 x 150 ml bottle.
25 x 50 ml bottle.
12 x 100 ml bottle
12 x 150 ml bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Like all parenteral products, the vials and bottles of Optiray should be inspected visually for integrity of the container. Optiray vials and bottles are intended for single use only. Discard any unused solution immediately.

7 MARKETING AUTHORISATION HOLDER

Guerbet
BP 57400
95943 Roissy CdG cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0686/007/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd April 1993

Date of latest renewal: 22nd April 2008

10 DATE OF REVISION OF THE TEXT

March 2021