

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Optiray 160 mg I/ml Solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ioversol 339 mg/ml (equivalent to Iodine content of 160 mg/ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

Clear, colourless to pale faint yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Optiray 160 is a non-ionic X-ray contrast medium that is indicated for intra-arterial digital subtraction angiography (IA-DSA).

4.2 Posology and method of administration

Adult: Recommended dosage schedule.

<u>Procedure</u>	<u>Dosage*</u>	<u>Maximum Total Dosage</u>
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Adults:

Intra-arterial Digital Subtraction Angiography	5-80 ml	250 ml
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*Repeated as necessary.

Children: Safety and effectiveness of Optiray 160 in children have not yet been established.

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

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

Discard if the solution is markedly discoloured or is not clear of particulate matter.

Optiray 160 is supplied in single dose containers; discard any unused solution.

4.3 Contraindications

Use in patients with suspected or proven hypersensitivity to iodine-containing contrast media. Manifest hyperthyroidism.

4.4 Special warnings and precautions for use

As with all other X-ray contrast media, Optiray 160 may cause anaphylaxis or other manifestations of allergy including nausea, vomiting, dyspnoea, erythema, urticaria and hypotension. An increased risk of such reactions is associated with patients who have a history of increased sensitivity to iodine, or known allergies or hypersensitivity. In such patients, the benefit should clearly outweigh the risks. Appropriate resuscitation measures should be immediately available. Serious or fatal reactions, such as anaphylactic shock, cardiac failure, and apnoea, have been associated with the administration of iodine-containing radiopaque media. It is of the utmost importance to be completely prepared to treat any contrast medium reaction.

Serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord, or cardiac catheterization. A cause-effect relationship to the contrast medium has not been established, since the patient's pre-existing condition and procedural techniques are causative factors in themselves.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, or anuria, particularly when large doses are administered. In isolated cases, acute renal failure has been reported in those patients.

In patients with monoclonal gammopathy (multiple myeloma, Waldenström's macro-globulinaemia), diabetes mellitus and sickle cell disease, intravascularly administered iodine-containing radiopaque contrast media are potentially hazardous. In such patients, substantial deterioration in renal function is avoided if the patient is well hydrated before Optiray 160 administration. Iodine-containing contrast media may also be hazardous in patients known or suspected of having pheochromocytoma when administered intravascularly, and in patients with hyperthyroidism or with an autonomously functioning thyroid nodule.

Special caution should be exercised in patients with multiple myeloma or other paraproteinaemia diseases. The observed anuria in myelomatous patients has been suspected to result from the combination of both the intravascularly administered contrast agent and dehydration. The risk in myelomatous patients is not a contraindication to the procedure, but maintenance of normal hydration and close monitoring are required.

Intravascular administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If the possible benefit of the procedure outweighs the considered risks, the amount of radiopaque medium then applied should be kept to the absolute minimum. The blood pressure should be monitored throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out 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, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). Patients should be well hydrated prior to and following the administration of Optiray 160.

The possibility that a serious reaction may occur should always be considered. Increased risk is associated with a history of asthma or of a previous reaction to a contrast medium, a known sensitivity to iodine and known allergies or hypersensitivities. Severe idiosyncratic reactions have occurred. Pre-testing cannot be relied upon to predict severe reactions. A thorough medical history with emphasis on allergy and hypersensitivity may be more accurate in predicting potential adverse reactions. A positive history of allergies or hypersensitivity is not a contraindication, but

does require caution. Pre-medication with antihistamines or 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.

General anaesthesia may be indicated in selected patients. However, a higher incidence of adverse reactions has been reported, probably due to the hypotensive effect of the 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 suggested. The inhibitory effects of non-ionic X-ray contrast media on mechanisms of haemostasis have been shown, *in vitro*, to be less than that of conventional ionic contrast media at comparable concentrations. For this reason, standard angiographic catheters should be flushed frequently and prolonged contact of blood with the contrast agent in syringes and catheters should be avoided.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing 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.

X-ray examination of women should be conducted as far as possible during the pre-ovulation phase of the menstrual cycle.

In patients who are known epileptics or have a history of epilepsy, anticonvulsant therapy should be maintained before and following myelographic procedures. In some instances, anticonvulsant therapy may be increased for 48 hours before the examination.

Care should be taken in those patients receiving neuroleptic and anti-depressant therapy who require myelographic investigations. If possible these drug types should be withdrawn for at least 48 hours before the myelographic examination.

Re-examination should be delayed for 5 - 7 days, because re-exposure to iodinated contrast agents at short notice has been associated with an increased risk of adverse effects.

4.5 Interaction with other medicinal products and other forms of interaction

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

Acute renal failure has been associated with lactic acidosis in patients receiving Metformin at the time of an X-ray investigation involving parenteral administration of iodinated contrast media. Therefore, in patients in whom any such study is planned, Metformin should be withheld for at least 48 hours prior to and 48 hours subsequent to the procedure.

The result 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 contrast media. However, thyroid functions tests not depending on iodine estimations, e.g. T3 resin uptake and total or free thyroxine (T4) assays are not affected.

No other drug should be mixed with Optiray 160.

4.6 Fertility, pregnancy and lactation

There is no evidence that this product is safe during pregnancy, nor is there evidence in animal work, that it is free from hazard. The product should not be used during pregnancy unless benefit outweighs risk and is considered essential by the physician.

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 nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Adverse effects associated with Optiray are generally independent of the dose administered. In the majority of cases they are mild or moderate but very rarely can be serious or life-threatening. However, even mild adverse events may be the first indication of a serious, general reaction that occur rarely after iodinated X-ray contrast media. Contrast medium related hypersensitivity reactions may occur with a delay of some hours up to several days.

Adverse reactions may be classified as follows:

- a. Hypersensitivity reactions: 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. Patients with a history of allergic reactions are at increased risk of developing hypersensitivity reaction. Other type 1 (immediate) reactions such as 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 catheterization e.g. angina pectoris, ECG changes, cardiac arrhythmias, conductive disorders and coronary spasm, which 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 e.g. rashes, swelling, vasospasm and inflammation.
- g. Extravasation can cause serious tissue reactions, the extent of which is dependant on the amount and strength of the contrast solution in the tissue.

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.

Psychiatric disorders:

Very rare (<0.01%) Amnesia; anxiety; somnolence.

Nervous system disorders:

Rare (0.01%-0.1%) Dizziness; paraesthesia; tremor.

Very rare (<0.01%) Agitation; confusion; convulsion; disorientation; dyskinesia; dysphasia; hypoaesthesia; muscle cramps; paralysis; speech disorders; stupor.

Eye disorders:

Very rare (<0.01%) Conjunctivitis; transient cortical blindness; visual disorders.

Ear and labyrinth disorders:

Very rare (<0.01%) Tinnitus.

Cardiac disorders:

Rare (0.01%- 0.1%) Tachycardia.

Very rare (<0.01%) Palpitations; arrhythmias; atrial fibrillation; bradycardia; cardiac arrest; circulatory failure; ECG changes; extrasystole; heart block; ventricular fibrillation.

Vascular disorders:

Rare (0.01%-0.1%) Hypotension.

Very rare (<0.01%) Cerebrovascular disorders; cyanosis; hypertension; syncope; thrombophlebitis; vasodilation; vasospasm.

Respiratory, thoracic and mediastinal disorders:

Rare (0.01%-0.1%) Cough; dyspnoea; rhinitis.

Very rare (<0.01%) Apnoea; bronchospasm; hypoxia; laryngeal oedema; pharyngitis; pulmonary oedema; stridor.

Gastrointestinal disorders:

Occasional (0.1%-1%) Nausea; vomiting.

Rare (0.01%-0.1%) Taste perversion; dry mouth.

Very rare (<0.01%) Sialoadenitis; hypersalivation; tongue oedema; dysphagia; diarrhoea.

Skin and subcutaneous disorders:

Occasional (0.1%-1%) Urticaria.

Rare (0.01%-0.1%) Erythema; pruritus; rash.

Very rare (<0.01%) Angioedema; toxic epidermal necrolysis.

Renal and urinary disorders:

Rare (0.01%-0.1%) Painful/difficult micturition.

Very rare (<0.01%) Incontinence; acute renal failure; BUN increase; abnormal renal function; decreased creatinine clearance; haematuria; oliguria.

General disorders & administration reactions:

Very common (>10%) Hot flushes.

Common (1%-10%) Pain.

Rare (0.01%-0.1%) Pharyngeal oedema; chills; headache.

Very rare (<0.01%) Anaphylactic shock; facial oedema; periorbital oedema; fever; oedema; pallor; chest pain; abdominal pain; asthenia/fatigue; abnormal crying; injection site reactions; sweating increased.

4.9 Overdose

Overdoses are potentially fatal and usually affect the lungs and cardiovascular system. Treatment should be symptomatic. Dialysis can be used to remove Optiray 160 from the blood as Optiray 160 does not bind to plasma or serum protein.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Optiray 160 is a non-ionic X-ray contrast medium. Intravascular injection of Optiray 160 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 160, together with its hydrophilic properties and a low level of binding to serum and plasma proteins, indicate that Optiray 160 is distributed within the extracellular fluid space and eliminated relatively quickly throughout the kidneys by glomerular filtration. The mean half-lives after doses of 50 ml and 150 ml were 118 and 105 minutes respectively. Elimination via the faeces is negligible. $T_{1/2}$ is prolonged in renal failure. No significant metabolism, deiodination or biotransformation of Optiray 160 occurs.

5.3 Preclinical safety data

There were no findings in the preclinical testing of Optiray 160 which could be of relevance of the prescriber in recognising the safety of this product used for the authorised indications, and which is not already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tromethamine
Tromethamine hydrochloride
Sodium calcium edetate
Water for injections
Sodium hydroxide and hydrochloric acid may be used for adjustment of pH

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
Chemical and physical in-use stability has been demonstrated for 24 hours up to 37°C.

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. Do not freeze.

6.5 Nature and contents of container

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

Pack sizes:
10 x 50 ml bottle.

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 bottles of Optiray should be inspected visually for integrity of the container. Optiray bottles are intended for single use only. Discard any unused solution immediately.

7 MARKETING AUTHORISATION HOLDER

Covidien (UK) Commercial Ltd
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Whiteley
Fareham
Hampshire PO15 7NY
UK

8 MARKETING AUTHORISATION NUMBER

PA 1679/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 22nd April 2008

10 DATE OF REVISION OF THE TEXT

January 2012