

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

OPTIRAY[®]
Ioversol Injection

OPTIRAY[®] 240
Ioversol Injection 51% w/v, 240 mgI/mL

OPTIRAY[®] 300
Ioversol Injection 64% w/v, 300 mgI/mL

OPTIRAY[®] 320
Ioversol Injection 68% w/v, 320 mgI/mL

OPTIRAY[®] 350
Ioversol Injection 74% w/v, 350 mgI/mL

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OPTIRAY®
Ioversol Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravascular injection or subarachnoidal	Solution for injection, 240 mgI/mL, 300 mgI/mL, 320 mgI/mL, and 350 mgI/mL	Edetate Calcium Disodium USP, Hydrochloric Acid NF, Sodium Hydroxide NF, Tromethamine HCl, Tromethamine USP. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Adults

Optiray 350 administered intravascularly is recommended in **adults** for coronary arteriography and ventriculography, peripheral and visceral arteriography, intravenous contrast enhancement in computed tomography of the head and body, excretory urography, intravenous digital subtraction angiography and venography.

Optiray 320 administered intravascularly is recommended for angiography throughout the cardiovascular system in **adults**. The uses include cerebral, coronary, peripheral, visceral and renal arteriography, aortography and left ventriculography. Optiray 320 is also recommended for contrast enhanced computed tomographic imaging of the head and body and in excretory urography.

Optiray 300 administered intravascularly is recommended for use in **adults** for cerebral angiography, aortography, peripheral and visceral arteriography, intravenous contrast enhancement of computed tomography of the brain and body, excretory urography, intravenous digital subtraction angiography and venography.

Optiray 240 administered intravascularly is recommended for use in **adults** for cerebral angiography, venography, excretory urography as was contrast enhanced

computed tomographic imaging of the head and body. Optiray 240 is indicated for **subarachnoid administration** in adults for lumbar, thoracic, and cervical myelography.

Pediatric

Optiray 350 administered intravascularly is indicated in **children** for angiocardiology.

Optiray 320 administered intravascularly is recommended in **children** one year of age or over for angiocardiology, contrast enhanced computed tomography of the head and body and for excretory urography.

Optiray 300 administered intravascularly is recommended in **children** one year of age or over for intravenous excretory urography and intra-arterial digital subtraction angiography.

CONTRAINDICATIONS

Optiray is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

Optiray should not be administered to patients with clinically significant impairment of both hepatic and renal function.

WARNINGS AND PRECAUTIONS

WARNINGS

USE THE RECOMMENDED OPTIRAY CONCENTRATION FOR THE PARTICULAR PROCEDURE TO BE UNDERTAKEN.

A. General

Serious or fatal reactions have been associated with the administration of all iodine containing radiopaque media, including Optiray. It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate facilities and appropriate personnel be readily available in case a severe reaction should occur.

A previous reaction to a contrast medium of different chemical structure or a history of iodine sensitivity is not an absolute contraindication to the use of Optiray. However, extreme caution should be exercised in injecting these patients and prophylactic therapy

(as with corticosteroids for example) should be considered (see **PRECAUTIONS, General**).

There must be a clear indication for performing procedures involving the administration of contrast agents in all patients.

Patients with a history of allergy, bronchial asthma or other allergic manifestations, combined renal and hepatic disease, the elderly, debilitated or severely ill patients, those with homocystinuria, endotoxemia, elevated body temperature, severe hypertension or congestive heart failure, other cardiovascular disease, hyperthyroidism and recent renal transplant recipients, as well as patients sensitive to iodine, present an additional risk and call for careful evaluation of the risks involved against the benefits expected.

Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms 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.

Patients with a serum creatinine level above 3 mg/dL should not undergo excretory urography or other radiological procedures unless the benefits clearly outweigh the risks incurred.

In patients with advanced renal disease, iodinated contrast media should be used with caution and only when the examination is essential since excretion of the medium is impaired. Use of Optiray is not recommended in patients with anuria or severe oliguria.

Administration of radiopaque materials to patients known or suspected to have pheochromocytoma should be performed with extreme caution if, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks. The amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure and measures for treatment of a hypertensive crisis should be available.

General anaesthesia may be indicated in some procedures; however, one should be aware of possible increased incidence of adverse reactions in such circumstances.

Thyroid dysfunction

Optiray, like all other iodinated contrast media, may induce changes in thyroid function in some patients. Transient hyperthyroidism or hypothyroidism has been reported following iodinated contrast media administration to adult and pediatric patients. Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or even more than a month (see ADVERSE REACTIONS). Some patients were treated for hypothyroidism (see PRECAUTIONS – Pediatric Use- Infants).

B. Vascular Use

Intravascularly administered iodine-containing contrast media are potentially hazardous.

Non-ionic iodinated contrast media, including Optiray, inhibit blood coagulation less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes, catheters or tubes containing non-ionic contrast media. Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both non-ionic and ionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, number of injections, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including: close attention to keeping guidewires, catheters and all angiographic equipment free of blood; use of manifold systems and/or three way stopcocks; frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. Non-ionic iodinated contrast media are not recommended as flush solutions. The use of plastic syringes in place of glass syringes has been reported to decrease, but not eliminate, the likelihood of clotting.

Extreme caution should be used in patients who are known to have multiple myeloma and other paraproteinemias, because of the risk of inducing transient to fatal renal failure. In these instances, anuria has developed resulting in progressive uremia, renal failure, and eventually death. A minimal diagnostic dose should be employed and renal function, as well as extent of urinary precipitation of the myelomatous protein, should be monitored for a few days subsequent to the procedure. The patients should be normally hydrated for the examination, since dehydration may predispose to precipitation of myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect.

Intravascular administration of contrast media may promote sickling in individuals who are homozygous for sickle cell disease. Fluid restriction is not advised in these patients.

Optiray, as with other contrast medium, can cause serious neurologic sequelae, including permanent paralysis, following cerebral arteriography and injection into vessels supplying the spinal cord. The injection of a contrast medium should never be made following the administration of vasopressors, since they strongly potentiate neurologic effects.

C. Subarachnoid Use

Care is required to prevent inadvertent intrathecal administration of contrast medium. As an intrathecally administered medication, Optiray can enter the brain substance, which may increase the risk of adverse events associated with the procedure. Such adverse events may be delayed and life-threatening.

Myelography should not be performed when lumbar puncture is contraindicated – as in the presence of local or systemic infection where bacteremia is likely.

Myelography should be performed only in hospitalized patients under close medical observation, which is to be continued for 24 hours following the procedure.

Patients receiving anticonvulsants should be maintained on this therapy. Should a seizure occur, intravenous diazepam or phenobarbital is recommended. In patients with a history of seizure who are not on anticonvulsant therapy, premedication with barbiturates should be considered. Optiray should be used in epileptics only if a water soluble contrast medium is considered essential.

Prophylactic anticonvulsant treatment with barbiturates should be considered in patients with evidence of inadvertent intracranial entry of a large bolus of contrast medium, since there may be increased risk of seizure in such cases.

Gravitational displacement of a concentrated bolus of Optiray above the level of C₁ and especially into the intracranial subarachnoid spaces is to be avoided.

PRECAUTIONS

A. General

All procedures utilizing contrast media carry a definite risk of producing severe, life threatening, and fatal reactions. Therefore, the need for the examination should always

be carefully assessed and the risk-benefit factor should always be carefully evaluated before such a procedure is undertaken.

At all times, a fully equipped emergency cart – or equivalent supplies and equipment – and personnel competent in recognizing and treating adverse reactions of all severity should be immediately available. If a serious reaction should occur, immediately discontinue administration and institute appropriate treatment. 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.

The reported incidences of adverse reactions to contrast media are twice as high in patients with a history of allergy than in the general population. Patients with a history of previous reactions to a contrast medium or iodine are three times more susceptible than other patients. Most adverse reactions to contrast agents appear within one to 30 minutes after the start of injection, but delayed reactions may occur.

Before a contrast medium is injected, the patient should be questioned for a history of bronchial asthma or allergy.

Although a history of allergy may imply a greater than usual risk, it does not arbitrarily contraindicate the use of the medium.

The possibility of an idiosyncratic reaction in patients who have previously received a contrast medium without ill effect should always be considered. A positive history of bronchial asthma or allergy, a family history of allergy, or a previous reaction of hypersensitivity to another contrast agent warrant special attention. Such a history, by suggesting proneness to reactions, may be more accurate than pre-testing in predicting the potential for reaction, although not necessarily the severity or type of reaction in the individual case. A positive history of this type does not arbitrarily contraindicate the use of a contrast agent, when a diagnostic procedure is thought essential, but calls for caution.

The sensitivity test most often performed is the slow injection of 0.5 to 1.0 mL of the radiopaque medium, administered intravenously, prior to injection of the full dose. It should be noted that the absence of a reaction to the test dose does not preclude the possibility of a reaction to the full dose. Severe reactions and fatalities have occurred with the full dose after a non-reactive test dose, and with or without a history of allergy.

Prophylactic therapy with corticosteroids should be considered for patients who present with a strong allergic history, a previous reaction to a contrast medium, or a positive

pre-test (since in these patients the incidence of reaction is two to three times that of the general population). Adequate doses of corticosteroids should be started early enough prior to contrast medium injection to be effective and should continue through the time of injection and for 24 hours after injection. Corticosteroids should not be mixed in the same syringe with the contrast medium because of chemical incompatibility.

Renal failure has been reported in patients with liver dysfunction who were given an oral cholecystographic agent followed by an intravascular iodinated radiopaque agent and also in patients with occult renal disease, notably diabetics and hypertensives. Administration of Optiray should be postponed in patients with hepatic or biliary disorders who have recently taken a cholecystographic agent. An interval of at least 48 hours should be allowed between examinations, especially in patients with reduced renal reserve. Prior to contrast medium administration, these patients should be well hydrated, since dehydration is the single most important factor influencing further renal impairment.

Acute renal failure has been reported in patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with pre-existing renal disease) following administration of iodinated contrast agents. Careful consideration of the potential risks should be given before performing radiographic procedures with Optiray in these patients.

B. Intravascular

Reports of thyroid storm following intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be carefully evaluated in such patients before use of Optiray.

Special precaution is advised in patients with increased intra-cranial pressure, cerebral thrombosis or embolism, primary or metastatic cerebral lesions, subarachnoid hemorrhage, arterial spasm, transient ischemic attacks, and in any condition when the blood-brain barrier is breached or the transit time of the contrast agent material through the cerebral vasculature is prolonged, since clinical deterioration, convulsions, and serious temporary or permanent neurological complications (including stroke, aphasia, cortical blindness, etc.) may occur following intravenous or intra-arterial injection of relatively large doses of contrast media. Such patients, and patients in clinically unstable or critical condition, should undergo examinations with intravascular contrast

media only if, in the opinion of the physician, the expected benefits outweigh the potential risks; in such circumstances, the dose should be kept to the absolute minimum.

When considering the use of high doses of contrast media, caution should be exercised in patients with congestive heart failure because of the transitory increase in circulatory osmotic load. Such patients should be kept under surveillance for several hours in order to detect delayed hemodynamic disturbances.

There have been reports in the literature indicating that patients on adrenergic beta-blockers may be more prone to severe adverse reactions to contrast media. Treatment of allergic-anaphylactoid reactions in these patients is more difficult. Adrenaline should be administered with caution, since it may not exert its usual effects. Larger doses of adrenaline may be needed to overcome the bronchospasm, however, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart-block, and possible potentiation of bronchospasm. Alternatives to the use of large doses of adrenaline include vigorous supportive care (i.e., fluids and beta agonists, such as parenteral salbutamol or isoproterenol) to overcome bronchospasm and norepinephrine to overcome hypotension.

In angiographic procedures, the presence of a vigorous pulsatile flow should be established before using a catheter or pressure injection technique. A small "pilot" dose of about 1 to 2 mL should be administered to locate the exact site of needle or catheter tip to help prevent injection of the main dose into a branch of the aorta or intramurally. Great care should be taken to avoid the entry of a large concentrated bolus into an aortic branch.

Mesenteric necrosis, acute pancreatitis, renal shutdown, serious neurologic complications including spinal cord damage and hemiplegia or quadriplegia have been reported following inadvertent injection of a large part of the aortic dose of contrast media into an aortic branch or arterial trunks providing spinal or cerebral artery branches.

Pulsation must be present in the artery to be injected. Extreme caution is advised in considering peripheral angiography in patients suspected of having thromboangiitis obliterans (Buerger's disease) since any procedure (even insertion of needle or catheter) may induce a severe arterial or venous spasm. Caution is also advisable in patients with severe ischemia associated with ascending infection. Special care is required in patients with suspected thrombosis, ischemic disease, local infection or a significantly

obstructed vascular system. Occasional serious neurologic complications, including paraplegia, have been reported in patients with aorto-iliac or femoral artery bed obstruction, abdominal compression, hypotension, hypertension and following injection of vasopressors.

When large individual doses are administered an appropriate time interval should be permitted to elapse between injections to allow for subsidence of hemodynamic disturbances. Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Following catheter procedures, gentle pressure hemostasis is advised followed by immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture.

Intravenous Contrast Enhancement in Computed Tomography

Following injection of relatively large doses of contrast media used in the procedure, transient or permanent neurological changes have been reported.

C. Subarachnoid Use

Elderly patients may be at a greater risk of adverse events following myelography. The need for the procedure in these patients should be evaluated carefully. Special attention must be given not to exceed the recommended dose of the contrast medium, to ensure the patient is sufficiently hydrated, and to ensure proper and sterile radiographic technique.

If grossly bloody CSF is encountered, the possible benefits of a myelographic procedure should be considered in terms of the risk to the patient.

Experience with the use of water-soluble contrast media in myelography indicates that, in most cases of major motor seizure, one or more of the following factors were present, and should, therefore, be avoided:

- Deviations from recommended procedure on myelographic management;
- Use in patients with a history of epilepsy;
- Inadvertent overdosage;
- Intracranial entry of a bolus or premature diffusion of a high concentration of the medium;
- Medication with neuroleptic drugs or phenothiazine antinauseants;

- Failure to maintain elevation of the head during and after the procedure;
- Active patient movement or straining.

Repeat procedures: If in the clinical judgment of the physician a repeat examination is required, an interval of 5 days between procedures is recommended.

Special precautions to be observed when performing specific diagnostic procedures are listed in the **DOSAGE AND ADMINISTRATION** section.

Special Populations

Pregnant Women: No teratogenic effects attributable to Optiray have been observed to date in studies performed in animals. There are no studies on the use of Optiray in pregnant women. Many injectable contrast media cross the placental barrier in humans and appear to enter fetal tissue passively. Optiray probably crosses the placental barrier in humans by simple diffusion to reach fetal tissue. Optiray should be used during pregnancy only if the benefit to the mother clearly outweighs the risk to the fetus. It should be borne in mind that X-ray procedures involve a certain risk related to exposure of the fetus.

Nursing Women: Because contrast media are secreted in human milk, if the administration of Optiray is considered to be essential, breastfeeding should be discontinued for at least 48 hours following the procedure.

Pediatrics (0-18 years of age): Some pediatric patients have a higher risk of adverse reactions to contrast media. Such patients may include those with sensitivity to allergens, including other drugs, those with asthma, congestive heart failure, a serum creatinine >1.5 mg/dL, or ages under 12 months.

Infants: Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or more than a month (see ADVERSE REACTIONS). Hypothyroidism in infants may be harmful for growth and development, including mental development and may require treatment. Thyroid function in infants exposed to ICM should therefore be evaluated and monitored until thyroid function is normalized.

Geriatrics (>65 years of age): The tolerance of elderly patients to drugs in general is diminished. These patients may have reduced renal reserve, impaired general health and may be taking medication (e.g. adrenergic B-blockers) that make them more susceptible to the potentially harmful effects of procedures involving the use of contrast media. The need for and the expected benefits of the procedure have to be carefully evaluated. Dosage should be very conservative.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Optiray is an iodinated contrast agent with an adverse reaction profile similar to other non-ionic contrast media. Adverse events associated with the use of any contrast agent may occur with Optiray.

Most adverse reactions following the use of Optiray are of mild or moderate intensity, however, serious, life-threatening and fatal adverse reactions, mostly of cardiovascular origin, have been reported.

Although most adverse reactions occur soon after the administration of the contrast medium, some adverse reactions can be delayed and can be of long-lasting nature.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible to adverse reactions than other patients.

The incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia, or myocardial infarction, may occur during coronary arteriography and left ventriculography. Adverse reactions to specific procedures are also discussed under **DOSAGE AND ADMINISTRATION**.

Injection of Optiray, as with other contrast media, is commonly associated with sensations of warmth and pain.

Clinical Trial Adverse Drug Reactions

Table 1 lists reactions based upon phase II and III clinical trials with Optiray formulations in 1506 adult patients to support the marketing authorization application. These adverse reactions are listed regardless of their direct attributability to the drug or the procedure and are coded according to the MedDRA (ver. 19.1) system organ classes.

Table 1 - Clinical Trial Adverse Drug Reactions Supporting Marketing Authorization

System	Adverse Reactions*
Cardiac disorders	angina pectoris arrhythmia

System	Adverse Reactions*
	atrioventricular block complete bradycardia vascular trauma**
Ear and labyrinth disorders	vertigo
Eye disorders	periorbital oedema vision blurred
Gastrointestinal disorders	nausea vomiting
General disorders and administration site conditions	chills extravasation face oedema injection site haematoma malaise
Injury, poisoning and procedural complications	vascular pseudoaneurysm
Musculoskeletal and connective tissue disorders	muscle spasms
Nervous system disorders	aphasia cerebral infarction dizziness dysgeusia headache paresthesia presyncope
Psychiatric disorders	disorientation visual hallucination
Respiratory, thoracic and mediastinal disorders	coughing dyspnoea hypoxia laryngeal oedema nasal congestion pulmonary oedema sneezing
Skin and subcutaneous tissue disorders	pruritus urticaria
Vascular disorders	arterial spasm flushing hypertension hypotension

* Less Common Adverse Drug Reactions with a frequency of less than or equal to 1%.

** Adverse reaction with no equivalent preferred term in MedDRA version 19.1.

Controlled clinical trials with Optiray formulations supporting marketing authorization involved 128 patients for pediatric angiocardigraphy, contrast enhanced computed tomography of the head and body, and intravenous excretory urography. The adverse reactions reported were as follows: pyrexia (1.6%), nausea (0.8%), muscle spasm (0.8%), LV pressure change (0.8%).

Post-Market Adverse Drug Reactions From Clinical Trials

Table 2 lists additional reactions observed during the post-approval phase II and III clinical trials with Optiray formulations in 2370 adult patients. These adverse reactions are listed regardless of their direct attributability to the drug or the procedure and are coded according to the MedDRA (ver. 19.1) system organ classes.

Table 2 - Post-Market Adverse Drug Reactions From Clinical Trials

System	Adverse Reactions
Cardiac disorders	atrioventricular block cardiac arrest cardiovascular disorder myocardial infarction nodal rhythm palpitations
Ear and labyrinth disorders	tinnitus
Eye disorders	Conjunctivitis allergic
Gastrointestinal disorders	abdominal pain dry mouth dysphagia
General disorders and administration site conditions	asthenia chest pain fatigue injection site pain pyrexia
Infections and infestations	rhinitis
Injury, poisoning and procedural complications	heart injury
Investigations	blood pressure decreased ECG ST segment depression
Metabolism and nutrition disorders	acidosis
Musculoskeletal and connective tissue disorders	back pain muscular weakness
Nervous system disorders	brain mass somnolence tremor
Psychiatric disorders	anxiety hallucination
Renal and urinary disorders	micturition urgency polyuria renal pain urinary retention
Respiratory, thoracic and mediastinal disorders	hyperventilation pulmonary embolism

Skin and subcutaneous tissue disorders	erythema hyperhidrosis rash
Vascular disorders	vasodilatation vasospasm

Cumulative frequency from all clinical trials was 1.3% for nausea. Controlled post-approval clinical trials with Optiray formulations involved 183 pediatric patients. Pyrexia and nausea remained the most commonly reported adverse events following angiocardiology, contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography.

In addition to the above reported reactions, the following adverse reactions have been identified during post-market use of Optiray:

Endocrine disorders: Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to adult and pediatric patients, including infants. Some patients were treated for hypothyroidism.

Eye disorders: transient cortical blindness

General disorders and administrative site conditions: injection site reactions (rash, erythema, swelling, induration, bruising, nerve injury)

Immune system disorders: anaphylactic/hypersensitivity reaction and anaphylactoid reaction (mild to moderate manifestations such as but not limited to rash, erythema, asthenia, pallor, angioedema and peripheral edema); anaphylactic shock and anaphylactoid shock (with multi-organ failure and cardio-respiratory arrest which may be fatal); Type I hypersensitivity, Type IV hypersensitivity

Renal and urinary disorders: toxic nephropathy (such as contrast-induced nephropathy)

Respiratory, thoracic and mediastinal disorders: bronchospasm, laryngospasm, pharyngeal edema

Skin and subcutaneous tissue disorders: acute generalized exanthematous pustulosis (AGEP), erythema multiforme (EM), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

The following may occur with any contrast agent, including Optiray:

Allergic Type Reaction: apnea, bullous or pleomorphic rashes, cyanosis, edema of glottis, erythematous, lacrimation, purpura

Blood and lymphatic system disorders: disseminated intravascular coagulation, neutropenia

Cardiac disorders: atrioventricular block, bundle branch block, cardiogenic shock, cardiovascular

insufficiency, coronary artery thrombosis, cyanosis

Eye disorders: blindness, lacrimation increased

Gastrointestinal disorders: diarrhea

General disorders and administration site conditions: death

Immune system disorders: allergic type reactions, anaphylactic reaction

Musculoskeletal and connective tissue disorders: musculoskeletal stiffness

Nervous system disorders: coma, convulsion, dysgeusia, hemiparesis, hemiplegia, motor dysfunction, nystagmus, paralysis

Psychiatric disorders: confusional state, photomas, psychotic disorder, restlessness

Renal and urinary disorders: anuria, hematuria, oliguria, proteinuria, renal failure

Respiratory, thoracic and mediastinal disorders: apnea, laryngeal oedema

Skin and subcutaneous tissue disorders: purpura, rash erythematous

Vascular disorders: circulatory collapse, hypertensive crisis, hypotensive shock, thrombophlebitis, vasodilatation, venous and arterial thrombosis

Related to procedure: arterial spasm, brachial plexus palsy following axillary artery injections, dislodgment of atheromatous plaques, dissection of blood vessels, ecchymosis and tissue necrosis, hematoma, hemorrhage, injury to nerves and neighbouring organs, perforation, rupture, thrombophlebitis, thrombosis embolization

TREATMENT OF ADVERSE REACTIONS TO CONTRAST MEDIA

A guideline for the treatment of adverse reactions is presented below. This outline is not intended to be a complete manual on the treatment of adverse reactions to contrast media or on cardio-pulmonary resuscitation. The physician should refer to the appropriate texts on the subject.

It is also realized that institutions or individual practitioners will already have appropriate systems in effect and that circumstances may dictate the use of additional or different measures.

For Minor Allergic Reactions (if considered necessary)

The intravenous or intramuscular administration of an antihistamine, such as diphenhydramine HCl 25 to 50 mg, is generally sufficient (contraindicated in epileptics). The resulting drowsiness makes it imperative to ensure that out-patients do not drive or leave the hospital unaccompanied.

Major or Life-threatening Reactions

A major reaction may be manifested by signs and symptoms of cardiovascular collapse, severe respiratory difficulty, and nervous system dysfunction. Convulsions, coma, and cardio-respiratory arrest may ensue.

The following measures should be considered:

1. Start emergency therapy immediately - carefully monitoring vital signs.
2. Have emergency resuscitation team summoned - do not leave patient unattended.
3. Ensure patent airway - guard against aspiration.
4. Commence artificial respiration if patient is not breathing.
5. Administer oxygen, if necessary.
6. Start external cardiac massage in the event of cardiac arrest.
7. Establish route for i.v. medication by starting infusion of appropriate solution (5% dextrose in water).
8. Judiciously administer specific drug therapy as indicated by the type and severity of the reaction. Careful monitoring is mandatory to detect adverse reactions of all drugs administered:
 - a) Soluble hydrocortisone 500 to 1000 mg i.v. for all acute allergic anaphylactic reactions
 - b) Adrenaline 1: 1000 solution (in the presence of anoxia it may cause ventricular fibrillation; **use caution** in patients on adrenergic beta blockers) (*see PRECAUTIONS*)
 - i. 0.2 to 0.4 mL subcutaneously for severe allergic reactions
 - ii. in extreme emergency 0.1 mL per minute, appropriately diluted, may be given intravenously until desired effect is obtained. Do not exceed 0.4 mL
 - iii. in case of cardiac arrest 0.1 to 0.2 mL, appropriately diluted, may be given intracardially
 - c) In hypotension (carefully monitoring blood pressure):
 - i. Phenylephrine HCl 0.1 to 0.5 mg appropriately diluted slowly i.v. or by slow infusion

OR

- ii. Noradrenalin 4 mL of 0.2% solution in 1000 mL of 5% dextrose by slow drip infusion

- d) Sodium bicarbonate 5%, 50 mL i.v. every 10 minutes as needed to combat post-arrest acidosis
 - e) Atropine 0.4 to 0.6 mg i.v. to increase heart rate in sinus bradycardia. May reverse 2nd or 3rd degree block
 - f) To control convulsions:
 - i. Pentobarbital Sodium 50 mg in fractional doses slowly i.v. (contraindicated if cyanosis is present)
 - OR
 - ii. Diazepam 5 to 10 mg slowly i.v. titrating the dose to the response of the patient
9. Defibrillation, administration of antiarrhythmics and additional emergency measures and drugs may be required.
10. The patient should be transferred to the intensive care unit when feasible for further monitoring and treatment.

DRUG INTERACTIONS

Drugs which lower seizure threshold, especially phenothiazine derivatives, including those used for their antihistaminic or anti-nauseant properties, should not be used with Optiray.

Renal toxicity has been reported in patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Therefore, administration of a contrast agent should be postponed by at least 48 hours following use of an oral cholecystographic agent.

DOSAGE AND ADMINISTRATION

A. General

Only the lowest dose necessary to obtain adequate visualization should be used.

Use only the recommended concentration for the particular procedure to be undertaken.

Patients should be well hydrated prior to and following administration of Optiray (ioversol). Do not dehydrate patients for any procedure.

Optiray should be inspected visually for particulate matter and discoloration prior to administration. If either is present, the vial should be discarded.

Optiray should not be transferred into other delivery systems except immediately before use, and should be used immediately once the seal has been punctured.

It is advisable that Optiray be at, or close to, body temperature when injected.

Under no circumstances should other drugs be administered concomitantly in the same syringe or i.v. administration set as Optiray because of a potential for chemical incompatibility.

Patency of the vessel and the position of the catheter tip or needle should be checked with a small pilot dose of Optiray before injecting the full dose. The catheter tip should be kept free of aspirated blood. Prolonged contact of Optiray with blood must be avoided because of potential thromboembolic complications.

The volume of each individual injection is a more important consideration than the total dose used. When large individual volumes are administered, sufficient time should be permitted to elapse between each injection to allow for subsidence of hemodynamic disturbances.

Any unused portion of one container should be discarded.

B. Intravascular Dosage and Administration

1. Cerebral Angiography

Optiray 320, 300 or 240 may be used to visualize the cerebral vasculature.

Patient Preparation - Suitable premedication may be given. Introduction of the catheter or needle is normally performed with local anaesthesia. General anaesthesia is rarely required (*see PRECAUTIONS, General*).

Precautions - In addition to the general precautions previously described, cerebral angiography with Optiray should be used with caution in elderly patients or patients in poor clinical condition. Additionally, caution is warranted in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis, embolism or subarachnoid hemorrhage, recent migraine, and any condition compromising the integrity of the blood brain barrier. Cerebral angiography with Optiray should only be used in these patients if the examination is considered to be necessary for the welfare of the patient. The patient should be watched carefully for possible adverse reactions.

Adverse Reactions - The major sources of cerebral arteriographic adverse reactions to Optiray appear to be related to repeated injections of the contrast material,

administration of doses higher than those recommended, the presence of occlusive atherosclerotic vascular disease, and the method and technique of injection.

Since non-ionic contrast media have no significant anticoagulant properties, meticulous technique is necessary to avoid thromboembolic complications (*see* **WARNINGS**).

A feeling of warmth in the face and neck is frequently experienced. Infrequently, a more severe burning discomfort is observed. Transient visual hallucinations have been reported.

Serious neurological reactions that have been associated with cerebral angiography include, stroke, seizures, amnesia, hemiparesis, visual field loss, cortical blindness, aphasia, confusion, disorientation, hallucination, convulsions, coma, and death.

Cardiovascular reactions that may occur with Optiray are: bradycardia, arrhythmia, change in systemic blood pressure, and ECG changes.

The EEG changes associated with the use of contrast media, including Optiray, for cerebral arteriography are common. Optiray can be expected to have the same effect on the electrophysiology of the brain, but this has not been systematically assessed.

Adult Dosage and Administration - Optiray 240, 300 or 320 may be used for cerebral angiography. The usual adult dosage of Optiray employed varies with the site and method of injection, and the age and condition of the patient. The usual adult dose range for common carotid arteriography is 5 to 10 mL; for vertebral arteriography it is 4 to 8 mL. For aortic arch injection (four vessel studies), the usual dose for Optiray 320 is 15 to 25 mL, and for Optiray 240 is 15 to 40 mL. Injections should be made at rates approximately equal to the flow rate of the vessel being injected.

These doses may be repeated if indicated. The total dose per procedure should be limited to the smallest volume necessary to achieve a diagnostic examination and should not exceed 200 mL.

2. Intra-Arterial Digital Subtraction Artetiography

Optiray 300 is a suitable agent for intra-arterial digital subtraction angiography (IA-DSA). With this technique, lower iodine concentrations can yield diagnostic images. Other advantages of the procedure are the use of less contrast medium and a decreased need for selective arterial catheterization. However, with aortic injection, visualization of small vessels may be insufficient.

Patient Preparation - No special patient preparation is required for IA-DSA. However, patients should be normally hydrated prior to examination.

Precautions - In addition to the general precautions already described, the risks and adverse reactions associated with IA-DSA are those usually associated with the conventional procedure performed in the area of the specific vessel.

In IA-DSA of the distal aorta, great care is necessary to avoid entry of a large aortic bolus into an aortic branch, since this could cause deleterious effects on the organs supplied by the branch. Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Adverse Reactions - Adverse reactions seen with IA-DSA are similar to those observed during peripheral arteriography and may occur due to trauma during the procedure.

Adverse reactions reported with the use of iodinated contrast media include hypotension, soreness in extremities, transient arterial spasm, gangrene, perforation of vessels, extravasation, hemorrhage, hematoma formation with tamponade, injury to nerves and other structures in close proximity to the artery, thrombosis, dissecting aneurysm, arteriovenous fistula, dislodgment of atheromatous plaques, subintimal injection and transient leg pain from contraction of calf muscles in femoral arteriography.

Pediatric Dosage and Administration - The usual pediatric dose of Optiray 300 for IA-DSA is 1 to 3 mL/kg.

3. Peripheral Arteriography

Optiray 350, 320 or 300 may be used for arteriograms of the lower extremities.

Patient Preparation - The procedure is normally performed with local anesthesia. General anesthesia usually is not required (*see PRECAUTIONS, General*).

Precautions - In addition to the general precautions previously described, moderate decreases in blood pressure occur frequently with intra-arterial injections. This change is usually transient; however, the blood pressure should be monitored for approximately 10 minutes following injection.

Injection of Optiray in patients with severe arterial disease (e.g. thromboangiitis obliterans, severe atherosclerosis, ischemia, thrombosis, significant obstruction) should be undertaken with extreme caution and only when absolutely necessary.

When injections are being made in the distal aorta for aorto-iliac run-off studies, the possibility of inadvertent injection of a large dose into a branch of the aorta or intramural dissection should be considered.

To prevent extravasation or subintimal injection, the position of the catheter tip or needle should be carefully evaluated. Fluoroscopy is recommended. **Pulsation must be present in the artery to be injected.** A small dose of 1 to 2 mL should be administered to locate the exact site of the needle or catheter tip. Great care is necessary to avoid entry of a large bolus into an aortic branch.

Severe pain, paresthesia, or peripheral muscle spasm during injection may require discontinuance of the procedure and a re-evaluation of the catheter tip or needle placement.

Following catheter procedures, gentle pressure hemostasis is advised, followed by observation and immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture.

Adverse Reactions - Adverse reactions observed during peripheral arteriography may be due to trauma during the procedure or to the injection of the contrast material. Adverse reactions reported with the use of iodinated contrast media include: hypotension, soreness in extremities, transient arterial spasm, contrast medium induced thrombosis, embolism, gangrene, perforation of vessels, extra-vasation, hemorrhage, hematoma formation with tamponade, injury to spinal cord and nerves and other structures in close proximity to the artery, transverse myelitis, thrombosis, dissecting aneurysm, arteriovenous fistula, dislodgment of atheromatous plaques, subintimal injection, leg pain, and renal damage including infarction and tubular necrosis due to accidental filling of the renal arteries.

Adult Dosage and Administration - The usual single adult dose for aorto-iliac run-off studies is 20 to 50 mL; for iliac and femoral arteries it is 10 to 30 mL. These doses may be repeated as indicated. The total procedural dose should be limited to the smallest volume required to obtain a diagnostic examination and should not usually exceed 250 mL.

4. Selective Coronary Arteriography with or without Left Ventriculography

Optiray 320 or 350 is recommended for selective coronary arteriography.

Precautions - Since the risk in coronary arteriography is increased if the procedure is performed shortly after acute myocardial infarction, it is recommended that this procedure not be performed for approximately 4 weeks following the diagnosis of myocardial infarction. Mandatory pre-requisites to the procedure are experienced personnel, ECG monitoring apparatus, and adequate facilities for immediate resuscitation and cardioversion.

Patients should be monitored continuously by ECG and vital signs throughout the procedure. The injection of relatively large volumes of hypertonic solutions (e.g. contrast media) into the heart chambers can cause significant hemodynamic disturbances. Caution is advised especially in patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly since it may induce serious arrhythmias.

Adverse Reactions - Most patients will have transient ECG changes during the procedure. The following adverse events have occurred in conjunction with the administration of iodinated intravascular contrast agents for coronary arteriography: hypotension, shock, anginal pain, coronary thrombosis, myocardial infarction, cardiac arrhythmias (bradycardia, ventricular tachycardia, heart block, ventricular fibrillation), cardiac arrest, and death.

Severe adverse reactions, especially arrhythmias, are likely to occur with greater frequency following right coronary artery injection. Fatalities have been reported. Complications to the procedures include: dissection of coronary arteries, dislodgement of atheromatous plaques, embolization from the catheter, perforation of heart chambers or coronary arteries with cardiac tamponade, hemorrhage, and thrombosis.

Adult Dosage and Administration - The usual adult dose range with Optiray 320 or Optiray 350 for left coronary arteriography is 2 to 10 mL and for right coronary arteriography is 2 to 6 mL. For left ventriculography, the usual single adult dose is 30 to 40 mL. These doses may be repeated if indicated; however, several minutes should be allowed to elapse between injections to allow for subsidence of hemodynamic disturbance, and the total procedural dose should be limited to the smallest volume necessary to obtain a diagnostic examination. The total procedural dose should not exceed 250 mL.

Pediatric Dosage and Administration - Optiray 320 and 350 are recommended for left coronary arteriography in children 1 year of age and over. The usual single injection

dose of Optiray 320 and 350 is 1.25 mL/kg with a range of 1 mL/kg to 1.5 mL/kg. When multiple injections are given, the total administered dose should not exceed 5 mL/kg up to a total volume of 250 mL.

5. Aortography and Visceral Arteriography

Optiray 300, 320 or 350 are recommended for aortography and visceral arteriography.

Precautions - Avoid entry of a large bolus into an aortic branch. Excessive dose injection of Optiray into an aortic branch or arterial trucks (i.e., those supplying the spinal arteries), or prolonged contact time between the concentrated contrast medium and the CNS tissue has been associated with adverse events, including: mesenteric necrosis, acute pancreatitis, renal infarction, acute tubular necrosis, renal shutdown, and serious neurologic complications (e.g. paraplegia and quadriplegia). Conditions that can contribute to prolonged contact time include: decreased circulation, aortic stenosis or partial occlusions distal to the site of injection, abdominal compression, hypotension, general anesthesia, or the administration of vasopressors. When these conditions exist or occur, the necessity of performing or continuing the procedure should be carefully evaluated and the dose and number of repeat injections should be maintained at a minimum with appropriate intervals between injections.

Adverse Reactions - Aortic injection of contrast medium may also be associated with the following adverse events: injury to the aorta and neighbouring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria due to accidental filling of the renal arteries, retroperitoneal hemorrhage from the translumbar approach, spinal cord injury, and pathology associated with the syndrome of transverse myelitis. Occasional serious neurological complications (e.g. paraplegia) have been reported in patients with aorto-iliac or femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressor drugs to enhance contrast. In such patients, the concentration, volume and number of injections should be kept to a minimum.

Adult Dosage and Administration - Optiray 300, 320 or 350 are recommended for aortography and visceral arteriography. The usual individual injection volumes are as follows:

abdominal aorta	20 to 50 mL
superior mesenteric artery	20 to 40 mL
renal artery	4 to 10 mL

Total procedural dose should not exceed 250 mL.

6. Intravenous Contrast Enhancement in Computed Tomography (CT)

Contrast enhancement should only be considered if unenhanced scans do not provide sufficient diagnostic information. Injection of contrast media may obscure certain lesions visible on unenhanced scans. The decision to employ contrast enhancement, which is associated with additional risk and increased radiation exposure, should be based upon a careful evaluation of the patient's clinical condition, renal and cardiac reserve, the status of the blood-brain barrier, and other radiological and unenhanced CT findings.

Warnings - Patients with diabetes mellitus, impaired renal function, and congestive heart failure are considered to be at greater risk of developing acute renal failure following injection of the large doses of contrast media required for contrast enhancement in CT scanning.

Convulsions and other serious neurologic complications (e.g. stroke) have occurred in patients with primary or metastatic cerebral lesions, breached blood-brain barrier, or slowed cerebral circulation, following the administration of iodine-containing radiopaque media for enhancement of CT brain images.

Patient Preparation - No special patient preparation is required for contrast enhancement in computerized tomography. **However, it has to be ensured that patients are well hydrated prior to examination.** In patients undergoing abdominal or pelvic examination, opacification of the bowel by dilute oral contrast medium may be valuable in scan interpretation.

Precautions - Patient motion, including respiration, can markedly affect image quality, therefore, patient cooperation is essential.

The use of an intravascular contrast medium can obscure some tumours in patients undergoing CT evaluation; this may result in a false negative diagnosis.

Computed Tomography of the Head

Neoplastic Conditions - Optiray 240, 300, 320 or 350 may be used to enhance the demonstration of the presence and extent of certain primary or metastatic malignancies.

The usefulness of contrast enhancement for the investigation of the retrobulbar space, and in cases of low grade or infiltrative glioma, has not been demonstrated.

In cases where lesions have calcified, there is less likelihood of enhancement. Following therapy, tumours may show decreased or no enhancement. Maximum contrast enhancement of certain tumours may be delayed necessitating delayed scans.

Non-Neoplastic Conditions - The use of Optiray 240, 300, 320 or Optiray 350 may be beneficial in the image enhancement of non-neoplastic lesions, such as cerebral infarctions of recent onset; however, some infarctions are obscured if contrast media are used.

Arteriovenous malformations and aneurysms will show contrast enhancement. In the case of these vascular lesions, the enhancement is probably dependent on the iodine content of the circulating blood pool.

Hematomas and intraparenchymal bleeders seldom demonstrate any contrast enhancement. However, in cases of intraparenchymal clot, for which there is no obvious clinical explanation, contrast medium administration may be helpful in ruling out the possibility of associated arteriovenous malformation (*see PRECAUTIONS*).

The opacification of the inferior vermis following contrast medium administration has resulted in false positive diagnoses in a number of normal studies.

Adult Dosage and Administration - The usual adult dosage of Optiray 300, 320 or 350 are 50 to 100 mL; for Optiray 240 it is 100 to 250 mL. A maximum dose of 150 mL of Optiray 320 or 350 should not be exceeded. For Optiray 240, the maximum dose is 250 mL. Scanning is usually performed immediately after injection.

Pediatric Dosage and Administration - The recommended dose of Optiray 320 for children one year of age and over is 1 mL/kg to 3 mL/kg.

Body Computed Tomography

Optiray 240, 300, 320 or 350 may be administered for contrast enhancement of the organs, tissues and larger blood vessels of the chest, abdomen and pelvis.

Continuous or multiple scans separated by intervals of 1 to 3 seconds during the first 30 to 90 seconds post-injection of the contrast medium (dynamic CT scanning) are required to demonstrate enhanceable lesions not seen with CT alone. Subsets of patients in whom delayed body CT scans might be helpful have not been identified.

Inconsistent results have been reported and abnormal and normal tissues are usually isodense during the time frame used for delayed CT scanning. At present, consistent results have been documented using dynamic CT techniques only.

Adult Dosage and Administration - Optiray 240, 300, 320 or 350 may be administered by bolus injection, rapid infusion, or a combination of both. Depending on the area to be examined, the usual dose range for infusion is 30 to 100 mL. When prolonged enhancement is required, 25 to 50 mL may be given as a rapid bolus and the remainder as an infusion. The total dose should not exceed 150 mL of Optiray 300, 320 or 350; or 200 mL of Optiray 240. Scanning is usually performed immediately after injection.

Pediatric Dosage and Administration - The recommended dose of Optiray 320 for use in children one year of age and over is 2 mL/kg, with a range of 1 mL/kg to 3 mL/kg. ,

7. Venography

Optiray 240, 300 or Optiray 350 may be used to visualize the peripheral venous circulation. Venograms are obtained by injection or infusion into an appropriate vein in the lower extremity.

Precautions - In addition to the general precautions previously described, specific caution is advised when venography is required in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a significantly obstructed venous system.

Extreme caution is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe venous disease.

Adverse Reactions - Complications of the procedure include: bleeding, thrombosis, embolism, contrast medium-induced thrombophlebitis, gangrene, and major systemic adverse reactions.

Adult Dosage and Administration - The usual adult dose of Optiray 240, 300 or 350 will range from 20 to 100 mL for the lower extremity.

Following the procedure, the venous system should be flushed with normal or heparinized saline solution. Massage and elevation of the leg are also helpful for clearing the contrast medium from the extremity to prevent post-procedural thrombophlebitis. The maximum dose should not exceed 250 mL.

8. Excretory Urography

Optiray 350, 320, 300 or 240 may be used for excretory urography. Following intravenous injection in patients with normal renal function, Optiray is excreted mostly by the kidneys. Maximum radiographic density in the calyces and pelves occurs in most instances within 5 to 15 minutes after injection.

Patient Preparation - A low residue diet the day preceding the examination, and a laxative the evening before the examination, may be given unless contraindicated.

Partial dehydration is dangerous and may contribute to acute renal failure. Maintenance of normal hydration is desirable.

Precautions - Adequate renal function must be present. Dehydration will not improve contrast quality in patients with impaired renal function and will increase the risk of contrast induced renal damage. The examination should not be repeated for at least 72 hours because of the potential of additive renal damage (*see WARNINGS and PRECAUTIONS*).

Adverse Reactions - All adverse reactions known to occur with the intravenous use of Optiray can also occur with excretory urography (*see ADVERSE REACTIONS*).

Adult Dosage and Administration - The usual adult dose of Optiray 300, 320 or 350 is 50 mL in the average normal adult. With Optiray 240 the equivalent dose is 65 mL in the average normal adult. In these patients, high dose urography may be preferred using Optiray 320 at a dose of 1.5 to 2 mL/kg. The dose is injected intravenously, usually within 1 to 3 minutes. Maximum doses of 200 mL of Optiray 240, 150 mL of Optiray 300 or 320 and 140 mL of Optiray 350 should not be exceeded.

Pediatric Dosage and Administration - Optiray 300 and Optiray 320 are recommended at a dose of 1 mL/kg and may range from 0.5 mL/kg to 3 mL/kg. Dosage for children over 1 year of age should be administered in proportion to age and body weight. The total administered dose should not exceed 3 mL/kg.

Table 3 – Adult Intravascular Dosage

Procedure	Concentration of Solution (mgI/mL)	Usual Recommended Single Dose (mL)
Cerebral angiography	320 300 240	
Common carotid		5 to 10

Procedure	Concentration of Solution (mgI/mL)	Usual Recommended Single Dose (mL)
Vertebral Aortic arch		4 to 8 15 to 25 (Optiray 320) 15 to 40 (Optiray 240)
Subtraction angiography		
Common carotid		5 to 10
Vertebral arteries		4 to 8
Aortic arch		20 to 35
Distal aorta		20 to 45
Iliac arteries		6 to 15
Peripheral arteriography	350 320 300	
Aorto-iliac run-off		20 to 50
Iliac and femoral arteries		10 to 30
Selective coronary Arteriography	320 350	
Left coronary		2 to 10
Right coronary		2 to 6
Left ventriculography		30 to 40
Aortography and visceral arteriography	300 320 350	
Abdominal Aorta		20 to 50
Superior Mesenteric Artery		20 to 40
Renal Artery		4 to 10
Intravenous Contrast Enhanced CT	240 300 320 350	
Head CT		50 to 100
Body CT		30 to 100 (infusion) 25 to 50 (bolus)
Venography	240 300 350	20 to 100
Excretory urography	240 300 320 350	65 50 50 50

Table 4 – Pediatric Intravascular Dosage

Procedure	Concentration of Solution (mgI/mL)	Usual Recommended Single Dose (mL/kg body weight)
Excretory urography	300	> 1 year old: 2 mL/kg
	320	> 1 year old: 1 to 1.5 mL/kg
Intra-arterial digital subtraction angiography	300	1 to 3 mL/kg
Pediatric angiocardiology	320	1 to 1.5 mL/kg
	350	
Computed tomography of the head	320	1 to 3 mL/kg
Computed tomography of the body	320	1 to 3 mL/kg

C. Subarachnoid and Dosage and Administration

Precautions - Optiray 240 is recommended for the examination of lumbar, thoracic, and cervical regions in adults by lumbar injection. Myelography should not be performed in the presence of significant local or systemic infection, where bacteremia is likely, or when lumbar or cervical puncture is contraindicated.

The volume and concentration of Optiray 240 to be administered will depend on the degree and extent of contrast required within the recommended dose range in the area under examination, and on the equipment and technique employed. Optiray 240 is slightly hypertonic to CSF.

A total dose of 3600 mg (15 mL) iodine should not be exceeded in adults. As in all diagnostic procedures, the minimum volume and dose to produce adequate visualization should be used. Most procedures do not require the total maximum dose.

Anesthesia is not necessary. Seizure-prone patients should be maintained on anticonvulsant medication.

Adverse Reactions - Any adverse reactions known to occur with the intravenous use of Optiray can also occur during myelography, especially those that originate in the CNS. In clinical trials, the most commonly observed adverse reaction was headache, which had an incidence of 8.6%.

Rate of injection: To avoid excessive mixing with CSF and consequential dilution of contrast medium, injection should be made slowly over 1 to 2 minutes.

Depending on the estimated volume of Optiray that may be required for the procedure, a small amount of CSF may be removed to minimize distension of the subarachnoid spaces, unless contraindicated.

The spinal puncture needle may be removed immediately following injection because it is not usually necessary to remove Optiray after injection into the subarachnoid space.

If a repeat examination is required, an interval of 5 days between procedures is recommended.

Adult Dose and Administration - The usual recommended total dose of Optiray 240 for use in lumbar myelography is 10 mL, and for thoracic and cervical myelography it is 15 mL.

If computerized tomography is to follow, it should be deferred for 2 to 6 hours to allow the amount of Optiray to decrease. Computerized tomography shows CSF contrast enhancement in the thoracic region in about one hour.

Patient Management – Subarachnoid Administration

Pre-procedure

- Discontinue neuroleptic drugs (including phenothiazines, e.g., chlorpromazine, prochlorperazine and promethazine) at least 48 hours beforehand.
- Maintain normal diet up to 2 hours before procedure.
- Premedication is not usually considered necessary.
- Should myelography be necessary in patients with a history of seizures, such patients should be maintained on their anticonvulsant medication.

During Procedure

- Use minimum dose required for satisfactory contrast (*see* **DOSAGE AND ADMINISTRATION**).
- In all positioning techniques, keep the patient's head elevated above highest level of spine.
- Do not lower head of table more than 15° during examination.
- In patients with excessive lordosis, consider lateral position for injection.
- Inject slowly (over 1 to 2 minutes) to avoid excessive mixing.
- Move medium within the spinal subarachnoid space under fluoroscopic monitoring. Avoid intracranial entry of a bolus.
- Avoid early and high cephalad dispersion of the medium.
- Avoid abrupt or active patient movement to minimize excessive mixing with CSF.

Instruct patient to remain passive. Move patient slowly and only as necessary.

Post-procedure

- Following myelography, move contrast medium to low lumbosacral area by upright positioning of the patient, for a few minutes.
- Before moving patient to stretcher, raise head of stretcher to at least 30°.
- Movement onto and off of the stretcher should be done slowly, with patient completely passive and maintaining a head up position.
- Before moving patient onto bed, raise head of bed from 30° to 45°.
- Maintain close observation and head-up position for at least 24 hours after myelogram.
- Encourage oral fluids and diet as tolerated.
- If nausea or vomiting occur, do not use phenothiazine antinauseants. Persistent nausea and vomiting will result in dehydration. Therefore, prompt consideration of fluid replacement by intravenous administration is recommended.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The adverse events of overdose are life-threatening and affect mainly the pulmonary, cardiovascular, and central nervous systems. Treatment of an overdose is directed toward the support of all vital functions, and prompt institution of specific therapy.

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

ACTION AND CLINICAL PHARMACOLOGY

A. General

The pharmacokinetics of Optiray in normal subjects conform to an open two compartment model with first order elimination (a rapid alpha phase of 6.8 minutes for drug distribution and a slower beta phase of 92 minutes, for drug elimination). Based on the blood clearance curves for 12 healthy volunteers (6 receiving 50 mL and 6 receiving 150 mL of Optiray 320), the biological half-life was 1.5 hours for both dose levels and there was no evidence of any dose related difference in the rate of elimination. The mean half-life for urinary excretion following a 50 mL dose was 118 minutes (105 to 156) and following a 150 mL dose was 105 minutes.

Optiray is excreted mainly through the kidneys following intravascular administration. Fecal elimination is 3 to 9%. Approximately 50% of the injected dose is excreted at 1.5 hours and 86% at 48 hours; about 1.5% is retained, mostly by the thyroid and liver. In patients with impaired renal function and in infants with immature kidneys, the elimination half-life is prolonged. In patients with severe renal disease, excretion does not occur.

Optiray does not notably bind to serum or plasma proteins to any marked extent and no significant metabolism, deiodination, or biotransformation occurs.

Optiray, like other non-ionic contrast media, has an insignificant effect on blood coagulation (as shown by slightly increased prothrombin time and partial thromboplastin time, and delayed platelet aggregation) and does not possess the anti-coagulant properties of ionic contrast media.

Optiray causes concentration-dependent hemolysis, aggregation, and crenation of red blood cells.

Elevations of several laboratory parameters (AST, ALT, LDH, bilirubin, creatinine and BUN) following intravascular administration have been reported in several patients, which were not considered clinically significant.

B. Intravascular

Intravascular injection of Optiray opacifies those vessels in the path of flow of the contrast bolus, permitting their radiographic visualization.

Following intravenous contrast medium administration, the increase in density in non-neural tissue is dependent on the presence of iodine in the vascular and extravascular (extra cellular) compartments. This is related to the rate and amount of contrast material administered, blood flow, vascularity, capillary permeability, extravascular effusion, and renal filtration.

Peak iodine blood levels occur immediately following rapid intravenous administration, then fall rapidly as the contrast medium is diluted in the plasma volume and diffuses from the vascular into the extravascular spaces. Equilibration between plasma and extravascular iodine concentration occurs within a few minutes.

Contrast enhancement (increase in the difference in density between adjacent tissues) is the result of differential vascular and extravascular iodine concentration between normal and abnormal tissues, which may accentuate inherent differences in pre-existent tissue density. With contrast enhancement, a pathological lesion may demonstrate increased or decreased density compared to the surrounding normal tissue. Some lesions, however, will remain or become isodense and thus undetectable by attempted contrast enhancement. Contrast enhancement in most cases is greatest immediately after bolus injection.

Optiray may be visualized in the renal parenchyma within 30 to 60 seconds following rapid intravenous injection. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1 to 3 minutes, with optimum contrast occurring within 5 to 15 minutes.

In nephropathic conditions, particularly when excretory capacity has been altered, the rate of excretion varies unpredictably, and opacification may be delayed for up to several hours after injection. Severe renal impairment may result in a lack of diagnostic opacification of the urinary tract, and depending on the degree of renal impairment, prolonged plasma ioversol levels may be anticipated in these patients as well as in infants with immature kidneys.

Optiray (32%I) was compared in intra-carotid studies in 45 anesthetized rats to iopamidol (33%I), iohexol (32%I) and diatrizoate (30%I). There was no detectable damage to the blood-brain barrier with any of these substances.

Generally, less warmth and pain are associated with the injection of Optiray than with conventional ionic media. Comparative studies using diatrizoate and iothalamate showed significantly less heat sensation and pain with Optiray. Other non-ionic agents, iohexol and iopamidol, gave results similar to Optiray.

Optiray had significantly less effect on cardiovascular and ECG parameters than did diatrizoate. For example, it produced significantly less bradycardia, tachycardia, T-wave changes, ST depression, ST elevation and hypotension than were seen with diatrizoate.

C. Subarachnoid

Following its injection into the subarachnoid space, ioversol mixes readily with the cerebrospinal fluid (CSF) and diffuses into root sleeves and upward in the spinal and intracranial subarachnoid spaces. The time it takes ioversol to reach the cervical and intracranial subarachnoid spaces will depend to a large degree on the patient's position and movements. As it diffuses upward, its concentration decreases.

Following lumbar subarachnoid injection, conventional radiography will continue to provide good diagnostic degree of contrast for at least 30 minutes. At about 1 hour, a diagnostic degree of contrast will usually not be available due to diffusion through the CSF and transfer to the general circulation.

D. Computerized Tomography

CT Scanning of the Head

In brain scanning, the contrast medium does not accumulate in normal brain tissue due to the presence of the blood-brain barrier. The increase in X-ray absorption in the normal brain is due to the presence of the contrast agent within the blood pool. A break in the blood-brain barrier, such as occurs in malignant tumors of the brain allows accumulation of the contrast medium within the interstitial tumor tissue; adjacent normal brain tissue does not retain the contrast medium.

Rapid infusion of the dose yields peak blood iodine concentrations immediately following infusion (within 15 to 120 seconds), which fall rapidly over the next 5 to 10 minutes.

Diagnostic contrast enhancement images of the brain have been obtained up to 1 hour after intravenous bolus administration.

CT Scanning of the Body

During CT of the body, Optiray diffuses rapidly from the vascular to the extra-vascular space. Increase in X-ray absorption is related to blood flow, concentration of the contrast medium, and extraction of the contrast medium by interstitial tissue. Contrast enhancement is thus due to the relative differences in extra-vascular diffusion between normal and abnormal tissue - a situation

quite different from that in the brain.

Contrast enhancement appears to be greatest immediately after bolus infusion (15 to 120 seconds).

Utilization of a continuous scanning technique (dynamic CT scanning) may improve enhancement of tumor and other lesions, such as an abscess.

STORAGE AND STABILITY

Store at controlled room temperature between 15° and 30° C. Discard unused portion. Submersion of syringes in water is not recommended. Do not re-autoclave plastic container because of possible damage to syringe. Protect from light and freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each millilitre of Optiray 240 (ioversol injection 51% w/v) provides 509 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. Optiray 240 provides 24% (240 mg/mL) organically bound iodine.

Each millilitre of Optiray 300 (ioversol injection 64% w/v) provides 636 mg of ioversol with 3.6 mg of tromethamine as buffer and 0.2 mg of edetate calcium disodium as a stabilizer. Optiray 300 provides 30% (300 mg/mL) organically bound iodine.

Each millilitre of Optiray 320 (ioversol injection 68% w/v) provides 678 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. Optiray 320 provides 32% (320 mg/mL) organically bound iodine.

Each millilitre of Optiray 350 (ioversol injection 74% w/v) provides 741 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. Optiray 350 provides 35% (350 mg/mL) organically bound iodine.

Optiray 320

30 mL vials, boxes of 10

50 mL vials, boxes of 10

100 mL fill/150 mL bottles, boxes of 10

150 mL bottles, boxes of 10

200 mL fill/250 mL bottles, boxes of 10

Ultraject power injector prefilled syringes of 75 mL fill/125 mL; 100 mL fill/125 mL and 125 mL, boxes of 10 and 20.

Optiray 350

50 mL vials, boxes of 10

100 mL fill/150 mL bottles, boxes of 10

150 mL bottles, boxes of 10

200 mL fill/250 mL bottles, boxes of 10

Ultraject power injector prefilled syringes of 100 mL fill/125 mL, boxes of 10 and 20.

Not all formats and packaging configurations are applicable for all global markets.

Pharmacy Bulk Vial for Optiray 320 and 350 (500 mL Bottle); Boxes of 5**For Multiple Dispensing**

This Bulk Pharmacy Vial is intended for multiple dispensing for intravenous use only, it must be spiked only once.

Directions for Use

Use proper aseptic techniques when handling injection device for maintenance of sterility during multiple dispensing contrast agent at room temperature.

The availability of the Bulk Pharmacy Vial is restricted to hospitals with a recognized intravenous admixture program for multiple dispensing.

Once punctured, use the contents of the Pharmacy Bulk Vial within four (4) hours and diluted solutions within 24 hours if kept at room temperature, and 72 hours if refrigerated from the time of initial puncture.

PART II: SCIENTIFIC INFORMATION

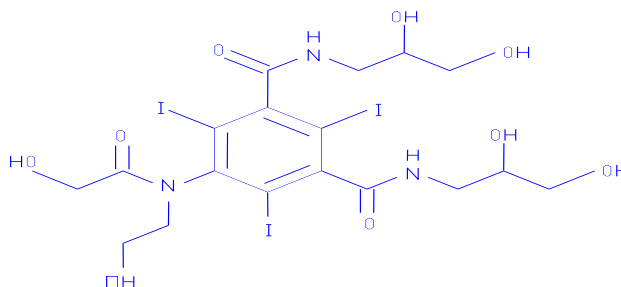
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ioversol

Chemical name: N,N'- Bis(2,3 -dihydroxypropyl)-5-[N -(2-hydroxyethyl)-glycolamido]-2,4,6-triiodoisophthalamide

Molecular formula and molecular mass: C₁₈H₂₄I₃N₃O₉, 807.12



Structural formula:

Physicochemical properties:

Optiray formulations are clear, colourless to pale yellow, sterile, non-pyrogenic aqueous solutions. Crystallization does not occur at room temperature.

The pH of the Optiray formulations is adjusted between 6.0 and 7.4 with hydrochloric acid or sodium hydroxide.

	Optiray 240	Optiray 300	Optiray 320	Optiray 350
Ioversol content (mg/mL)	509	636	678	741
Iodine content (mg/mL)	240	300	320	350
Osmolality (mOsm/kg)	502	651	702	792
Viscosity (cps)				
25°C	4.0	8.2	9.9	14.3
37°C	3.0	5.5	5.8	9.0

The product does not contain a preservative and is intended for single dose use only.

DETAILED PHARMACOLOGY

The biodistribution, metabolism and excretion of Optiray were evaluated in rats and dogs following intravenous injection of 0.2 and 2.0 g I/kg. For these studies, Optiray was exchange-labelled with ^{125}I and radioactivity was assayed in biological samples.

Following intravenous injection of two lots of ^{125}I ioversol into rats at dose levels of 0.2 and 1.0 g I/kg, 6 male and 6 female rats being used at each dose level, radioactivity was rapidly excreted, primarily via the urine. Two male and 2 female rats were killed at 2, 24 and 48 h for assay of radioactivity in organs, urine and feces. Seventy-three to 90% of the radio-activity had been excreted by 2 hours. By 24 hours, 91-99% of the injected dose was recovered in urine and feces, and approximately 1 % of the dose was retained by all assayed organs and tissues (thyroid 1.1 %, liver 0.5%). The experiment was repeated with 24 additional rats with similar results.

Following a single intravenous injection of ^{125}I ioversol in 12 conscious beagle dogs, 6 male and 6 female, the disappearance of radioactivity from blood was typically bi-exponential with an initial distribution half-life ranging from approximately 1 to 4 minutes followed by a terminal elimination phase with a half-life ranging from approximately 40-55 minutes. No significant organ retention of radioactivity was apparent after 48 hours and 86-88% of the radioactivity was excreted, primarily in the urine, within 48 hours. Fecal excretion amounted to about 3-9%. Upon reverse phase HPLC analysis, ioversol accounted for essentially all of the radioactivity excreted in the urine, suggesting that ioversol is excreted in an unchanged form in dogs.

The pharmacokinetics of ioversol intravascularly administered in normal human subjects conform to an open two compartment model with first order elimination (a rapid alpha phase for drug distribution and a slower beta phase for drug elimination). Based on the blood clearance curves for 12 healthy volunteers (6 receiving 50 mL and 6 receiving 150 mL of Optiray 320), the biological half-life was 1.5 hours for both dose levels and there was no evidence of any dose related difference in the rate of elimination.

Following intracisternal injection of ^{125}I -ioversol (240 mgI/kg) in 5 beagle dogs, 1 male and 4 female, activity was measured in the blood at 5 minutes and peaked at 3.9 hours post-injection. The elimination $t_{1/2}$ in the blood was 1.04 hours. The main route of excretion was in the urine, where 74% of the dose was recovered within 24 hours. By 72 hours post-injection, approximately 94% of the injected dose was eliminated in the urine and feces. Thus, elimination of ioversol injected into the cisterna magna was found to be fairly rapid and comparable to that reported for iopamidol in similar studies.

Four female beagle dogs received ioversol and 4 iopamidol. Plasma concentrations were assayed by HPLC and CSF and urine concentrations by UV spectrophotometry, Both contrast media appeared in the plasma 15 min. after injection. Peak concentrations were attained within 56 min. The contrast media then rapidly disappeared from the plasma, the elimination $t_{1/2}$ for ioversol being 1.37 hr. and for iopamidol 1.23 hr. Urinary excretion for ioversol and iopamidol respectively was 37% and 39% after 2 hours and 69% and 74% after 6 hours. The results show that intrathecal administration of the two contrast media is followed by rapid absorption into the plasma and prompt urinary excretion. The absorption and elimination patterns of the two media via the route of administration were identical.

Upon incubation with dog red blood cells, ioversol caused hemolysis ranging from 0% at 2.5%I to 61% at 18.5%I w/v. Crenation (70-100%) and aggregation of red blood cells occurred only at high levels of ioversol (10% and 18.5%I). The results of this study indicate that ioversol is compatible with dog red blood cells at clinically relevant intravascular doses. It is likely also to be compatible with human red blood cells.

Ioversol does not notably bind to serum or plasma proteins to any marked extent and no significant metabolism, deiodination or biotransformation occurs. Using gel exclusion chromatography, ioversol exhibited a low order of human plasma protein binding (9 to 13%), which is of no consequence from a clinical standpoint.

The effects on blood coagulation of Optiray were compared with those of iopamidol, iohexol, diatrizoate and ioxaglate at concentration up to 32 mgI/mL when mixed with plasma (1:10 v/v) from human volunteers. Coagulation parameters were measured by effects on activated partial thromboplastin time, prothrombin time and thrombin time, and platelet aggregation. Coagulation times were increased in a concentration-related manner with all of the contrast media.

Where significant differences existed, the prolongation of coagulation times was less with ioversol, iopamidol and iohexol than with the ionic agent diatrizoate. Optiray was not significantly different from iopamidol or iohexol in the coagulation parameters measured. Ioversol, iopamidol and iohexol were found to inhibit platelet aggregation less than diatrizoate and ioxaglate. These findings are in line with the known greater anticoagulant effect of ionic agents such as diatrizoate when compared to non-ionic agents.

Histamine release from rat peritoneal mast cells was found to be significantly less ($p < 0.01$) with ioversol, iohexol and iopamidol than with amidotrizoate. Transient

elevations of ASAT, ALAT, LDH, bilirubin, creatinine and BUN were seen in several human subjects, but these were not clinically significant.

Single does intracarotid administration of 2 mL ioversol (28%I) in anesthetized rats, 6 rats per treatment group (total 18), showed a 26% drop in mean arterial pressure, compared with a 3% increase after saline, and a 46% drop after diatrizoate (28%I). Heart rate was reduced by 12%-a value which did not differ significantly from the saline control (-0.42%) but was significantly different from the drop with diatrizoate (-26%). A 7% increase in respiratory rate did not differ significantly from the saline control but was significantly different from diatrizoate (-93%). The incidence of arrhythmias with ioversol was the same as with the saline control (2/6 rats). Damage to the bloodbrain barrier was evaluated in 18 rats (6 each with ioversol 28%I, diatrizoate 28%I or saline) by intracarotid injection of sodium Tc-99m) pertechnetate one minute after test substance administration and determining the Tc-99m brain/blood ratio one minute. Later, the Tc-99m retention index was three times greater for the sodium diatrizoate than for the Optiray and saline groups, indicating that Optiray did not alter the blood-brain barrier, whereas sodium diatrizoate caused disruption of the barrier integrity.

Ioversol and iopamidol were each injected intracisternally into 16 female rats at dose levels of 60, 120, 240 and 480 mgI/kg (4 rats for each concentration, 32 in all). Sedation and hyper-activity were alternating events which were seen during the first hour after injection. The animals recovered uneventfully overnight. Two animals at the 480 mgI/kg dose level of iopamidol displayed mild convulsions during the first hour after dosing, but none were seen in the ioversol group. Mild teeth gnashing was seen with 3 animals: 2 with ioversol at 480 mgI/kg and 1 with iopamidol at 240 mgI/kg. Drug-related weight losses were seen during a 48 hour post-injection period in 4/4 rats given ioversol and in 2/4 given iopamidol - a significant difference. Such weight losses are not uncommon in animals who are given contrast media while under general anesthesia. Thus, by the intracisternal route in rats, ioversol is not more toxic than iopamidol.

Ioversol 30%I was relatively well tolerated by 3 cynomolgus monkeys given a single dose of 0.2 mL/kg intrathecally. Ioversol caused muscular fasciculations and/or tremor in 2/3 animals during the first hour after injection. No convulsions or pre-convulsive activity were seen. There were no other adverse events, no deaths and no signs of adhesive arachnoiditis at necropsy 12 weeks after injection. Optiray, therefore, does not appear to be toxic at the above dose by this route.

Cardiovascular Effects

Ioversol (37%I) caused a transient positive inotrophy and bradycardia in the isolated perfused rabbit heart following a single bolus injection. At the highest dose level intracoronary injection of 4.0 mL caused fibrillation in 5/6 preparations with ioversol, 3/5 with iohexol and 4/6 with iopamidol. The coronary cardiotoxicity of ioversol in the isolated perfused rabbit heart was qualitatively and quantitatively similar to that of the other non-ionic X-ray contrast media, iohexol (35%I) and iopamidol (37%I). The non-ionic agents differed from diatrizoate (37%I) in that they were more liable to cause fibrillation at the 4.0 mL dose and to cause increases in contractile force, while the diatrizoate caused marked dose-related decreases.

The hemodynamic effects of intravenously injected 37%I ioversol and iopamidol, 35%I iohexol and 37%I sodium meglumine diatrizoate were compared in 16 pentobarbital anesthetized dogs (4 per compound). Changes were graded as minimal (1-10%), slight (11-20%), moderate (21-30%) or marked (>30%). The non-ionics, at doses of 1.2 and 4 mL/kg, caused minimal to slight perturbations of left ventricular pressure, myocardial contractility, heart rate and blood pressure. Diatrizoate, in contrast, caused markedly reduced contractility and lowering of left ventricular, systolic and diastolic pressures. Therefore, while the non-ionic caused only minimal to slight changes in cardiovascular parameters, those produced by diatrizoate were distinguishable because of their greater magnitude. It may therefore be concluded that non-ionic agents cause less cardiovascular perturbations than ionic agents.

The cardiotoxicity of 37%I ioversol and 37%I sodium meglumine diatrizoate were compared using left intra ventricular doses of 1 and 3 mL and selective coronary injection (left: 5 and 10 mL, right: 5 and 8 mL) in 16 pentobarbital-anesthetized, closed chest dogs, 4 per test substance. Each dog received doses of 1, 2 and 4 mL/kg. As before, changes were graded as minimal (1-10%), slight (11-20%), moderate (21-30%) or marked (30%). Thirty seconds after intra ventricular injection of 3 mL/kg, diatrizoate induced a fall in arterial pressure of 46 mmHg (32%) compared to a fall after ioversol of 23 mmHg (16%). The mean fall of arterial pressure 30 seconds after intra-coronary injections was: for the left coronary: ioversol-5.0 mmHg, diatrizoate -22mmHg; for the right coronary: ioversol-11.5 mmHg, diatrizoate -3mmHg. At 15 seconds following injection the means were: for the left coronary: ioversol-7.5 mmHg, diatrizoate -22 mmHg; for the right coronary: ioversol-11.5 mmHg, diatrizoate -24 mmHg. These effects were therefore minimal or slight with ioversol versus moderate with diatrizoate. Arrhythmias occurred with ioversol in 1/3 dogs with left coronary injections of 10 mL and in 3/3 with diatrizoate. With right coronary injections of 5 mL, 3/3 dogs had arrhythmias with both agents and one of the dogs fibrillated and dies following diatrizoate. After 8 mL, two out of 3 dogs died with fibrillation following right coronary artery injection with ioversol and 1/3 after diatrizoate injection. The incidence

of arrhythmias, consisting mainly of premature ventricular contractions and fibrillation, was similar for each compound. In clinical studies with ioversol and in 2 to 3 years' use in patients worldwide, no corresponding effects have been seen in humans.

TOXICOLOGY

Acute Toxicity

Route of Administration	Species (Total No., Sex)	Dose/Range (gI/kg)	LD ₅₀ (gI/kg)	Toxic Signs
Intravenous	Mouse (150 m, 50 f) plus: 20 saline controls 20 untreated controls	16-22	18.4	Hypoactivity and respiratory depression. Livers showed chronic granulomatous inflammation, with necrosis at two highest dose groups.
Intravenous	Rat (50 m, 50 f) plus: 20 saline controls	14-18	15	Hypactivity and respiratory depression (former resolved by 4 h and the latter by ½ h). Vacuolation of renal tubules. Convulsions in 4/20.
Intravenous	Dog, purebred beagle (6 m, 6f) plus: 4 untreated controls 4 saline controls	3-12	No deaths	At 12 gI/kg dose trembling, licking, urination, retching, vomiting and hematuria were seen (resolved by 30 mins.).
Intracisternal	Rat (50 m, 50 f) plus: 10 untreated controls 10 saline controls	0.4-1.2	1.10	Transient hypoactivity, grooming and chewing behaviour which lasted >4 h. 600 to 1200 mgI/kg caused immediate death: meningeal hemorrhage, considered due to technique, was seen in these rats.
Intracisternal	Dog, purebred beagle ioversol 240 1 m, 1 f; ioversol 160 1 m, 1 f; ioversol 240 1 m, 1 f; iopamidol 160 1m, 1 f; iohexol 240 1 m, 1f; iohexol 160 1 m, 1 f saline controls 1 m, 1 f	0.16-0.24	No deaths	No deaths, convulsions or pre-convulsant activity. Some lethargy noted in 2 ioversol-treated dogs during recovery period. Tremor seen in dogs of all treatment groups. Nystagmus noted in 1 ioversol dog and 1 iohexol dog. Respiratory depression in 1 iopamidol dog. The acute intracisternal toxicity of ioversol was thus comparable to that of iohexol and iopamidol.

Acute toxicity (contd.)

Route of Administration	Species (Total No., Sex)	Dose/Range (gI/kg)	Duration of Study (days)	Toxic Signs
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Intravenous	Mouse (48m, 48f) 64 mice in iohexol control group	3.0, 6.0, 12.0 Same doses for iohexol controls	Single dose. At 3, 7, 14 and 29 days after dosing, 8 mice were killed and autopsies for evidence of hepatotoxicity.	Significant degenerative changes were seen microscopically in the livers of some mice of all groups treated with both ioversol and iohexol. Subcapsular, granulomatous inflammation occurred in 4.7% of ioversol mice and 6.5% of iohexol mice and was most marked at the 12 gI/kg dose. Vacuolative hepato- cellular degeneration occurred only at this dose and was seen at day 3 only with incidences of 5/8 and 4/8 for ioversol and iohexol respectively. The changes were not seen at 29 days post- injection. It was concluded that both contrast agents showed a similar incidence of reversible hepatic toxicity in 50 to 60% of mice.
Intrathecal	Cynomolgus Monkey (3 m) plus: 2 saline controls	0.06	Monkeys were then observed for a period of 85 days prior to sacrifice and autopsy.	Muscular fasciculations were noted in the first hour in 2 monkeys. Whole body tremors occurred in 1 monkey 1 h after injection. No treatment-related body weight changes occurred. Hematology and clinical chemistry, values showed no significant changes. Microscopically, there were no treatment-related changes and there was no evidence of arachnoiditis.

Acute toxicity (contd.)

Acute EEG effects of intracisternal metrizamide, ioversol, iohexol and iopamidol in rats

Route of Administration	Species (Total No., Sex)	Dose/Range (mgI/kg)	Observations
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Intracisternal	Sprague-Dawley rats: 67 f	<p>5 rats per dose group</p> <p>Metrizamide; 60, 120, 240</p> <p>Ioversol, iohexol and iopamidol: 240, 480, 720</p> <p>7 saline controls</p>	<p>Metrizamide rats: hypoactivity pronounced and prolonged. Dose related fatalities: 1/5, 2/5 and 4/5 deaths at 60, 120 and 240 mgI/kg, respectively. All showed EEG abnormalities including abnormal slow wave activity, spike activity or both.</p> <p>Iopamidol rats: prolonged hypoactivity compared to controls. Two rats at 240 mgI/kg had clonic seizures. EEG abnormalities were dose related showing either abnormal slow waves, spikes or both.</p> <p>Iohexol rats: hypoactivity similar in magnitude to the saline controls, but slightly prolonged. Evident only at 480 & 720 mgI/kg. EEG patterns not different from saline controls except that 2 rats did not show normal alert patterns.</p> <p>Ioversol rats: similar changes to iohexol. Hypoactive for longer than saline controls. Few or no EEG abnormalities. At 480 mgI/kg, 1 rat showed abnormal slow wave and spike activity which appeared no different from changes seen in saline controls. At 720 mgI/kg all rats had normal EEGs.</p> <p>The fact that ioversol and iohexol showed little or no toxicity compared to the other two agents is attributed by the authors to their greater hydrophilicity. The least hydrophilic agent, metrizamide, showed the most neurotoxicity, iopamidol the second most and ioversol and iohexol, the least neurotoxic, had the highest hydrophilicity.</p>
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Subacute toxicity

Route of Administration	Species (Total No., Sex)	Daily Doses (gI/kg)	Duration of Study (days)	Toxic Signs
Intravenous	Rat (72 m, 72 f) 40 untreated controls 40 saline controls	0.2, 0.8, 3.2	28 (Recovery observations to 56 days)	No overt toxic manifestations noted. No effects on body weight gain, food or water consumption. No significant effects on clinical chemistry parameters. Microscopic changes consisted of minimal to moderate dose-related renal vacuolation at the 0.8 and 3.2 gI/kg/day dose levels. Renal vacuolation was not seen at lower dose levels or in any rats after 28 and 56 day recovery periods. It was concluded that ioversol showed a low order of toxicity.
Intravenous	Dog, purebred beagle (30 m, 30 f) plus: 12 untreated controls 12 saline controls	0.2, 0.8, 3.2	28	Dose-related emesis was seen during the dosing period of the study. No effects on body weight gain, food or water consumption. No effects on clinical chemistry parameters. Mild hepato-cellular vacuolation was noted at the 3.2 gI/kg/day dose level in 4/8 dogs. They were not seen in dogs at the end of an 8 week recovery period.

Subacute toxicity (contd.)

15 days plus 4 weeks subarachnoid study of ioversol 240 IN

Route of Administration	Species (Total No., Sex)	Dose Range (mgI/kg)	Observations
Subarachnoid (via cisterna magna)	Pure-bred beagles 20 m 20 f	18, 36, 100 on days 1, 4, 8, 11 and 15	<p>Each dose level was given to 5 m and 5 f with 5 m and 5 f as saline controls. Following the 15 day dosing period, the dogs were held for a further 4 weeks.</p> <p>No treatment-related mortalities occurred during this study. The body weight and food consumption of the dogs were not influenced by the treatment. The results of body temperature recordings, ECG and ophthalmological examinations did not indicate any test substancerelated variations.</p> <p>A slight to moderate increase in CSF protein level was seen at all dosage levels at the end of treatment period, but these increases did not reach pathological levels. The results of hematology, biochemistry and urinalysis tests were normal.</p> <p>Macroscopic examination revealed only a low incidence of hematoma at the injection site, comparable between treated and control animals.</p> <p>Microscopic examination confirmed above gross findings: muscular and subcutaneous hematomas at the injection sites were the only changes observed in the treated and control animals.</p> <p>It is concluded that the subarachnoid administration of ioversol 240 to beagle dogs at the given doses over 15 days did not induce any systemic toxicity.</p>

Laboratoire Guerbet
Aulany-sous- Bois
France
4/89

Subacute toxicity (contd.)

Route of Administration	Species (Total No., Sex)	Daily Doses (gI/kg)	Duration of Study (days)	Toxic Signs
Intravenous	Rat Sprague-Dawley (4 m, 6 f) i.e. 2 m, 3 f per dose group	2.0, 5.0	28 Dosing on days 1.5. Autopsy at 24 h (1 m, 2 f) or 28 days (1 m, 1 f) after last injection	No overt toxic signs. No significant effects on clinical chemistry (no evidence of nephro- or hepatotoxicity). Hematuria present 1 day after 5th injection in 3/3 rats in high dose group. Explanation unknown: presumed due to undetected cystitis. Microscopically there were no signs of hepatotoxicity. Mild diffuse vacuolation was seen in epithelial cells of proximal renal tubules 1 day after the 5 gI/kg dosing. This was not present at the autopsy on day 28 after dosing. It was concluded that ioversol showed a low order of toxicity.

Genetic Toxicology

Two *in vitro* mutagenicity and chromosomal aberration studies indicated that ioversol 32%I w/v solution, in doses 0.1 to 150 mL per plate, did not possess mutagenic activity. Incubation with ioversol 32%I did not transform *Salmonella typhimurium*, *Escherischia coli* or mouse lymphoma cells under non-metabolic, or metabolic activation conditions (using Arochlor® 1254-induced rat liver metabolic activation system). In addition, ioversol did not induce chromosomal aberrations in Chinese hamster ovary cells *in vitro* under both non-metabolic and metabolic activation conditions.

Reproductive Toxicology

Ioversol was given intravenously to 3 groups of 30 female rats at dose levels of 0.2, 0.8 and 3.2 gI/kg once daily during days 7 through 17 of pregnancy. Higher values for litter size in test groups (not statistically significant) were related to higher implantation rates. There was a dose-related tendency to reduced fetal weights which was significant compared to the controls but not between dosage groups. There was also a dose-related reduction in litter size and implantation rate and a higher pup mortality rate. There was a non-significant, dose-related increase in fetuses with skeletal abnormalities. Group mean incidences of malformations and visceral anomalies were unrelated to dosage.

Intravenous administration of ioversol to 3 groups of 20 male Sprague-Dawley rats daily from 9 weeks prior to mating and throughout the mating period did not affect mating performance.

Intravenous administration of ioversol to 3 groups of 30 female Sprague-Dawley rats at dose levels of 0.2, 0.8 and 3.2 gI/kg daily from 2 weeks prior to mating and throughout mating, pregnancy and lactation did not affect duration of gestation, pre- and post-implantation loss, litter size or mean litter weight. No treatment-related adverse events were noted in the F₁ or F₂ offspring. Although 3.2 gI/kg ioversol was a no-effect level in this study, at 4.8 gI/kg tremors, languid behaviour and polynea were noted. At 3.2 gI/kg/day some reduction in food intake was observed, with differences attaining statistical significance on days 1 to 6 post-partum; also a slight retardation of body weight gain during late gestation occurred. Also at this highest dosage level there was a reduction in litter size. Mean pup weight was also lower, which resulted in a reduction of litter weight from day 4 to day 21 post-partum. It was not considered that treatment with ioversol had any significant adverse events on the dam or resulting litter parameters at 0.2 or 0.8 gI/kg/day; neither were there any adverse events on the maturation of the F₁ generation.

Ioversol was given intravenously at doses of 0.2, 0.8 and 3.2 gI/kg/day to three groups of pregnant rabbits (total 54) once daily during days 6 through 18 of pregnancy, Ioversol treatment was well tolerated in the pregnant rabbits and no treatment-related visceral or skeletal abnormalities were noted in fetuses derived from those killed on day 29 of pregnancy.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**OPTIRAY[®]
Ioversol Injection**

Read this carefully before you start taking Optiray and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Optiray.

What is Optiray used for?

Optiray is an imaging agent used to visualize the blood vessels, the compartment of the heart, the brain, parts of the body, the kidney and the bladder. Optiray can also be used to visualize the spinal canal.

How does Optiray work?

Optiray is an iodine-based contrast agent that opacifies the vessels and create a contrast difference between tissues permitting the radiographic visualization.

Once Optiray is injected, your doctor will take an image of the area to be examined. The contrast difference between tissues will appear in the image and help your doctor make the diagnosis.

What are the ingredients in Optiray?

Medicinal ingredients: Ioversol

Non-medicinal ingredients: Edetate Calcium Disodium USP, Hydrochloric Acid NF, Sodium Hydroxide NF, Tromethamine HCl, Tromethamine USP.

Optiray comes in the following dosage forms:

Vials: 240 mgI/mL, 300 mgI/mL, 320 mgI/mL, and 350 mgI/mL

Prefilled Syringes: 240 mgI/mL, 300 mgI/mL, 320 mgI/mL, and 350 mgI/mL

Do not use Optiray if:

- You are hypersensitive to Optiray or any of the ingredients in the formulation or component of the container.
- You have clinically significant impairment of both hepatic and renal function.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Optiray. Talk about any health conditions or problems you may have, including if:

- You have previous reaction to a contrast agent or have a history of iodine sensitivity.
- You have bronchial asthma, homocystinuria, endotoxemia, elevated body temperature, severe hypertension, cardiovascular disease or hyperthyroidism.
- You have a serum creatinine level above 3 mg/d, a renal disease or have a recent renal transplant.

- You have pheochromocytoma (tumor), multiple myeloma (cancer) or the sickle cell disease.
- You receive administration of vasopressors, cholecystographic agent or adrenergic beta-blockers.
- You have local or systemic infection.
- You have a history of seizure or you are epileptics.
- You are a patient with obstructed vascular system issues (thrombosis, ischemic disease or Buerger's disease).
- You could be pregnant. If there is a need to consider Optiray during your pregnancy, your doctor will discuss the benefits and risks of giving it to you.
- You are breastfeeding. Contrast media are secreted in human milk, therefore breastfeeding should be discontinued for at least 48 hours following the procedure.

Thyroid function

Contrast media containing iodine, such as Optiray, may change thyroid activity in some patients, both in adults and infants. This may cause:

- Hypothyroidism (i.e. too little thyroid hormones in the blood)
- Or hyperthyroidism (i.e. too much thyroid hormones in the blood)

Thyroid function in infants

Contrast media containing iodine may cause hypothyroidism in infants, especially infants born too soon that:

- Can continue for several weeks to a month after treatment
- Can harm growth and development
- Can harm mental growth
- May require treatment
- Can cause symptoms such as:
 - Fatigue, shortness of breath, low heart rate
 - Reduced appetite, feeling cold, weight gain
 - Muscle stiffness

Contact your doctor if these symptoms happen to you or your infant.

Your doctor may order blood tests for your infant after treatment to follow thyroid hormone levels in the blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Optiray:

- Phenothiazine derivatives
- Cholecystographic contrast agents

How to take Optiray:

Optiray will always be used in a hospital or similar setting. It will only be administered to you

under the supervision of a health professional skilled and experienced in the particular procedure to be performed.

Usual dose:

Your doctor will determine the amount of Optiray to be used. The dose administered will depend on the procedure.

Overdose:

Overdose affect mainly the pulmonary, cardiovascular, and central nervous systems.

If you think you have taken too much **Optiray**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using Optiray?

These are not all the possible side effects you may feel when taking Optiray. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions. Side effects may include:

- Hypotension, hypertension, cardiac arrest, cardiovascular disorder, palpitation.
- Perception of noise or ringing in the ears.
- Inflammation of infection of the eyes, transient blindness, vision loss, lacrimation.
- Lack of thyroid hormone (hypothyroidism).
- Dry mouth, difficulty or discomfort swallowing, diarrhea.
- Abnormal physical weakness, abdominal pain back pain, chest pain, fatigue, injection site pain, fever, nausea.
- Coughing, nasal congestion, sneezing, irritation and inflammation of the nose.
- Headache, disorientation, brain mass, somnolence, involuntary muscle contraction and relaxation, anxiety, hallucination, coma, convulsion, confusional state, psychotic disorders.
- Distorsion of the sense of the taste.
- Musculoskeletal stiffness, motor dysfunction, involuntary eye movement, paralysis.
- Urge to urinate, production of abnormal large volumes of urine, renal pain, urinary retention, renal failure.
- Hyperventilation, pulmonary embolism, edema, coagulation, abnormal level of white cells, heart block, apnea.
- Itching, erythema, excessive sweat, rash.
- Vasodilation, vasospasm.
- Hypersensitivity or allergic reaction.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
 - By calling 1-866-234-2345 (toll-free);
 - By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9
- Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at controlled room temperature. Protect from light and freezing. Keep out of reach and sight of children.

If you want more information about Optiray:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#) or by calling 1-844-208-7620.

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