PRESCRIBING INFORMATION

Proprietary name:	OPTIRAY 160, 240, 300, 320, 350
Proper name:	Ioversol Injection 34%, Ioversol Injection 51%, Ioversol Injection 64%, Ioversol Injection 68%, Ioversol Injection 74%
Pharmacology classification:	Non-ionic, low osmolality, water soluble, radiopaque contrast medium for intravascular use.

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PRODUCT MONOGRAPH

OPTIRAY

(Ioversol Injection)

OPTIRAY 160

(Ioversol Injection 34%, 160 mgI/mL)

OPTIRAY 240

(Ioversol Injection 51%, 240 mgI/mL)

OPTIRAY 300

(Ioversol Injection 64%, 300 mgI/mL)

OPTIRAY 320

(Ioversol Injection 68%, 320 mgI/mL)

OPTIRAY 350

(Ioversol Injection 74%, 350 mgI/mL)

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Non-ionic, low osmolality, water soluble radiopaque

contrast medium for intravascular use.

Optiray 240 may be used in myelography.

ACTIONS AND CLINICAL PHARMACOLOGY

A. GENERAL

The pharmacokinetics of Optiray (ioversol) 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 (105-156) and following a 150 mL dose was 105 minutes.

Optiray is excreted mainly through the kidneys following intravascular administration. Fecal elimination is 3-9%. 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, deionization or biotransformation occurs.

Optiray, like all other contrast media, may induce changes in thyroid function in some patients, and elevation of thyroxine and/or TSH may be observed.

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. INTRA VASCULAR

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 30-60 seconds following rapid intravenous injection. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1-3 minutes, with optimum contrast occurring within 5-15 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 (33%I) was compared in intra-carotid studies in 45 anesthetized rats to iopamidol (32%) and iohexol (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 (ioversol) 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.

INDICATIONS AND CLINICAL USES

A. INTRAVASCULAR

Adults

Optiray 350 (ioversol 350 mgI/mL) 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 (ioversol 320 mgI/mL) 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 (ioversol 300 mgI/mL) 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 (ioversol 240 mgI/mL) 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 160 (ioversol 160 mgI/mL) is recommended for use in **adults** for intra-arterial digital subtraction agniography.

Pediatric

Optiray 300 (ioversol 300 mgI/mL) is recommended in **children** one year of age or over for intravenous excretory urography and intra-arterial digital subtraction angiography.

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

Optiray 350 is indicated in **children** for angiocardiography.

B. SUBARACHNOID

Adults

Optiray 240 (ioversol240 mgI/mL) is indicated for subarachnoid administration in adults for lumbar, thoracic and cervical myelography.

CONTRAINDICATIONS

Optiray (ioversol) should not be administered to patients with known or suspected hypersensitivity to ioversol or in cases of clinically significant impairment of both hepatic and renal function.

WARNINGS

USE THE RECOMMENDED OPTIRAY (IOVERSOL) 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 (ioversol). 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 homo cystinuria, 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.

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.

B. VASCULAR USE

Intravascularly administered iodine-containing contrast media are potentially hazardous.

Non-ionic iodinated contrast media, including Optiray (ioversol), 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 non-ionic and also with 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.

In patients who are known to have multiple myeloma and other paraproteinemias, because of the risk of inducing transient to fatal renal failure, extreme caution should be used. 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.

As with any contrast medium, including Optiray, serious neurologic sequelae, including permanent paralysis, can occur 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

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 activity who are not on anticonvulsant therapy premedication with barbiturates should be considered. Optiray (ioversol) 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 C_1 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, or situations which may arise as a result of the procedure, 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 intravascularly injected 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. Premedication with corticosteroids to avoid or minimize possible allergic reactions may be considered.

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. Especially in these classes of patients there should be no fluid restriction and every attempt made to maintain normal hydration, prior to contrast medium administration, 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 (ioversol) in these patients.

B. INTRAVASCULAR

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of a physician skilled and experienced in the particular procedure to be performed.

Reports of thyroid storm occurring 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, and 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, and 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. At the same time, 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. On the one hand larger doses of adrenaline may be needed to overcome the bronchospasm, while on the other,

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 such as fluids and the use of beta agonists including 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 1-2 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, hypo-tension, 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 homocystin-uria 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.

Use in Pregnancy

No teratogenic effects attributable to Optiray (ioversol) 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.

Use in Lactation

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

Pediatric Use

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.

Use in Elderly Patients

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) which 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 and dosage should be very conservative.

Drug Interactions

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

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholocystographic 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.

C. SUBARACHNOID USE

Elderly patients may present a greater risk 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 see that 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.

Any intrathecally administered medication including non-ionic contrast media such as Optiray (ioversol) can enter the brain substance which may increase the risk of adverse effects associated with the procedure. Such adverse reactions may be delayed and, in extremely rare cases, may be life-threatening. Careful patient and dose selection and proper patient management before, during and after the procedure are therefore imperative. Care is required in patient management to prevent inadvertent intracranial entry of a large bolus of contrast medium. Also, effort should be directed to avoid rapid dispersion of the medium (i.e., by active patient movement).

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, under individual paragraphs pertaining to said specific procedures.

ADVERSE REACTIONS

Since Optiray (ioversol) is an iodinated contrast agent with an adverse reaction profile similar to other non-ionic contrast media, all known adverse effects associated with the use of any contrast agent can 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.

It should be kept in mind that, 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 than other patients.

The incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. In those patients only who had coronary arteriography with Optiray, the incidence of angina was 1.2%. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

In a controlled clinical trial involving 30 pediatric patients undergoing angiocardiography, no adverse reactions were reported.

The following table of reactions is based upon clinical trials with Optiray formulations in 1506 patients, regardless of their direct attributability to the drug or the procedure.

Adverse reactions to specific procedures are also dealt with under Dosage and Administration.

ADVERSE REACTIONS SEEN WITH OPTIRAY

System	>1%	1%	Adverse Reactions
Cardiovascular		none	angina pectoris hypotension blood pressure fluctuation arterial spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive		none	nausea vomiting
Nervous		none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction disorientation paresthesia dysphasia muscle spasm syncope visual hallucination
Respiratory		none	laryngeal edema pulmonary edema sneezing nasal congestion coughing shortness of breath hypoxia
Skin		none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous		none	extravasation hematoma

shaking chills
bad taste
general pain

In addition to the above reported reactions, the following may occur with any contrast agent, including Optiray:

Cardiovascular System: hypoxia, heart block, bundle branch block, coronary thrombosis, cyanosis, hypertensive crisis, peripheral vasodilation, acute vascular insufficiency, circulatory collapse, hypotensive shock, cardiogenic shock.

Central Nervous System: Photomas, persistent blindness, taste perversion, anxiety, tinnitus, motor dysfunction, convulsion, somnolence, confusion, psychotic reaction, stiff neck, hemiparesis, hemiplegia, nystagmus, restlessness, tremors, aphasia, paralysis, coma and death.

Allergic Type Reaction: purpura, conjunctivitis, lacrimation, erythematous, bullous or pleomorphic rashes, laryngospasm, bronchospasm, apnea, cyanosis, edema of glottis, laryngeal edema, angioneurotic edema, peripheral edema, anaphylactic shock. These allergic type reactions can progress into anaphylaxis, coma and death.

Renal System: transient proteinuria, hematuria and rarely oliguria, anuria and renal failure.

Other reactions: diarrhea, dry mouth, pallor, venous and arterial thrombosis and rarely thrombophlebitis, rare cases of disseminated intravascular coagulation, neutropenia.

Pediatrics: in controlled clinical trials involving 128 patients for pediatric angiocardiography, contrast enhanced computed tomography of the head and body, and intravenous excretory urography, adverse reactions following the use of Optiray 320 were generally less frequent than with adults. Adverse reactions reported were as follows: fever (1.6%), nausea (0.8%), muscle spasm (0.8%), LV pressure change (0.8%).

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

TREATMENT OF ADVERSE REACTIONS TO CONTRAST MEDIA

Contrast media should be administered only by physicians thoroughly familiar with the emergency treatment of all adverse reactions to contrast media. The assistance of other trained personnel such as cardiologists, internists and anesthetists is required in the management of severe reactions.
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 25-50 mg is generally sufficient (contraindicated in epileptics). The resulting drowsiness makes it imperative to ensure that out-patients do not drive or go home 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. Rave 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 500-1000 mg i. v. for all acute allergic anaphylactic reactions

b) Adrenaline 1: 1000 solution (in the presence of anoxia it may cause ventricular fibrillation; CAUTION in patients on adrenergic beta blockers. See PRECAUTIONS).

i. 0.2-0.4 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.

ii in case of cardiac arrest 0.1-0.2 mL, appropriately diluted, may be given intracardially.

c) In hypotension (carefully monitoring blood pressure):

i) Phenylephrine HCl 0.1-0.5 mg appropriately diluted slowly i.v. or by slow infusion

OR

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 0.4-0.6 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 5-10 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 careunit when feasible for further monitoring and treatment.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The adverse effects of overdosage are life-threatening and affect mainly the pulmonary, cardiovascular and central nervous systems. Treatment of an over-dosage 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 dialysable.

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 (ioversol) 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. INTRA VASCULAR DOSAGE AND ADMINISTRATION

1. CEREBRAL ANGIOGRAPHY

Optiray 320, Optiray 300 or Optiray 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 performed with special caution in elderly patients, patients in poor clinical condition, patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis, embolism or subarachnoid hemorrhage, following a recent attack of migraine, and in any condition compromising the integrity of the blood brain barrier, and only 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 some frequency, but not necessarily with Optiray, are bradycardia, arrhythmia, either an increase or decrease in systemic blood pressure, and ECG changes.

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

Usual Adult Dosage

Either Optiray 240, Optiray 300 or Optiray 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 5-10 mL; for vertebral arteriography 4-8 mL. For aortic arch injection (four vessel studies) the usual dose for Optiray 320 is 15-25 mL, and for Optiray 240 is 15-40 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 ARTERIOGRAPHY

Optiray 160 and Optiray 300 are suitable agents 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. They may sometimes 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.

Usual Adult Dosage Using Optiray 160

As a general rule, the volume and concentration used for IA-DSA are about 50%, or less, of that used for conventional procedures. The actual dosage and flow rate will vary depending on the selectivity of the injection site and the area being examined. The following suggested volumes per injection are intended as a guide. Injections may be repeated if necessary.

It is advisable to inject at rates approximately equal to the flow rate of the vessel being injected.

Carotid Arteries	5 to 10 mL
Vertebral Arteries	4 to 8 mL
Aortic Arch	25 to 50 mL
Distal Aorta	25 to 50 mL
Iliac Arteries	6 to 15 mL

Dosage should not usually exceed 250 mL.

Usual dose in Children 1 Year of Age and Over Using Optiray 300

The usual dose is 1 to 3 mL/kg, depending on the area to be examined.

3. PERIPHERAL ARTERIOGRAPHY

Optiray 350, Optiray 320 or Optiray 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 intra-mural 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 1-2 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, renal damage including infarction and tubular necrosis due to accidental filling of the renal arteries.

Usual Adult Dosage

The usual single adult dose for aorto-iliac run-off studies is 20-50 mL; for iliac and femoral arteries 10-30 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

Either Optiray 320 or Optiray 350 is recommended for this procedure.

Precautions

Since the risk in coronary arteriography is increased if the procedure is performed shortly after acute myocardial infarction, some physicians recommend that this procedure should 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 effects have occurred in conjunction with the administration of iodinated intravascular contrast agents for this purpose: 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.

Usual Adult Dosage

The usual adult dose range with Optiray 320 or Optiray 350 for left coronary arteriography is 2-10 mL and for right coronary arteriography is 2-6 mL. For left ventriculography, the usual single adult dose is 30-40 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 Optiray 350 are recommended for this procedure in children 1 year of age and over. The usual single injection dose of Optiray 320 and Optiray 350 is 1.25 mL/kg of body weight 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 is recommended for this procedure. Great care is necessary to avoid all entry of a large bolus into an aortic branch. Mesenteric necrosis, acute pancreatitis, renal infarction, acute tubular necrosis, renal shutdown and serious neurologic complications, including paraplegia and quadriplegia, have been reported and may be attributable to an excessive dose being injected into an aortic branch or arterial trunks supplying the spinal arteries or to prolonged contact time of the concentrated contrast medium with the CNS tissue. Conditions which 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

With aortic injection, depending on the technique employed, the risks of this procedure also include the following: 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 and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Occasional serious neurological complications including 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, Optiray 320 or Optiray 350 is recommended for this procedure. The usual individual injection volumes are as follows:

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

Total procedural dose should not exceed 250 mL.

6. INTRAVENOUS CONTRAST ENHANCEMENT IN COMPUTED TOMOGRAPHY (CT)

Because unenhanced scanning may provide adequate information in the individual patient and the injection of contrast media may obscure certain lesions visible on the plain scan, contrast enhancement is usually performed only if the unenhanced scan has not provided sufficient information. 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 including stroke have occurred in patients with primary or metastatic cerebral lesions or 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 insured 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, resulting in a false negative diagnosis.

Computed Tomography of the Head

Neoplastic Conditions

Optiray 240, Optiray 300, Optiray 320 or Optiray 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 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. (Also see Precautions).

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

Usual Adult Dosage

For adults the usual dosage of Optiray 300, 320, or 350 is 50-100 mL; of Optiray 240,100 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

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

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 1-3 seconds during the first 30-90 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.

Usual Adult Dosage

Optiray 240, 300, 320 or 350 may be administered by bolus injection, rapid infusion or by a combination of both. Depending on the area to be examined, the usual dose range for infusion is 30 - 100 mL. When prolonged enhancement is required, 25-50 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

The dose recommended for use in children one year of age and over is 1 mL/kg to 3 mL/kg body weight of Optiray 320 with a usual dose of 2 mL/kg.

7. VENOGRAPHY

Optiray 240, 300 or 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.

Usual Adult Dosage

The usual adult dose of Optiray 240, 300 or 350 will range from 20-100 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 thrombo-phlebitis. The maximum dose should not usually 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.

In patients with severe renal impairment, contrast visualization may be substantially delayed, or may not occur at all.

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. (Also see WARNINGS and PRECAUTIONS.)

Adverse Reactions

All adverse reactions known to occur with the i.v. use of Optiray can also occur with excretory urography (see Adverse Reactions).

Usual Adult Dosage

The usual adult dose of Optiray 300, Optiray 320 or Optiray 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 1.5-2 mL/kg. The dose is injected intravenously, usually within 1-3 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

Optiray 300 and 320 at doses of 0.5 mL/kg to 3 mL/kg of body weight has produced diagnostic opacification of the urinary tract. The usual dose for children is 1 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.

ADULT INTRAVASCULAR DOSAGE TABLE

PROCEDURE	CONC. OF SOLUTION (mgI/mL)	USUAL RECOMMENDED SINGLE DOSE (mL)
Cerebral Angiography	320	
	300	
	240	
Common Carotid		5 - 10
Vertebral		4 - 8
Aortic Arch		15 - 25 (Optiray 320)
		15 - 40 (Optiray 240)
Intra-arterial digital Subtraction angiography	160	
Common Carotid		5 - 10
Vertebral Arteries		4 - 8
Aortic Arch		20 - 35
Distal Aorta		20 - 45
Iliac Arteries		6 - 15
Peripheral Arteriography	350	
	320	
	300	
Aorto-iliac Run-off		20 - 50
Iliac and Femoral Arteries		10 - 30
Selective Coronary Arteriography	320 350	
Left Coronary		2 - 10
Right Coronary		2 - 6
Left Ventriculography		30 - 40
PROCEDURE	CONC. OF SOLUTION (mgI/mL)	USUAL RECOMMENDED SINGLE DOSE (mL)

Aortography and Visceral Arteriography	300 320 350	
Abdominal Aorta		20 - 50
Superior Mesenteric Artery		20- 40
Renal Artery		4 - 10
Intravenous Contrast Enhanced CT	240 300 320	
Heat CT	350	50 - 100
Body CT		30 - 100 (infusion) 25 - 50 (bolus)
Venography	240 300 350	20 - 100
Excretory Urography	240 300 320 350	65 50 50 50

PEDIATRIC INTRAVASCULAR DOSAGE TABLE

PROCEDURE	CONC. OF SOLUTION (mgI/mL)	USUAL RECOMMENDED SINGLE DOSE (mL/kg body weight))
Excretory Urography	300	> 1 year old: 2 mL/kg
Intra-Arterial Digital Subtraction Angiography	300	1 - 3 mL/kg
Pediatric Angiocardiography	320 350	1 - 1.5 mL/kg
Computed Tomography of the Head	320	1 - 3 mL/kg
Computed Tomography of the Body	320	1 - 3 mL/kg
Excretory Urography	320	> 1 year old: 1 - 1.5 mL/kg

C. SUBARACHNOID DOSAGE AND ADMINISTRATION

Precautions

Optiray 240 (ioversol 240 mgI/mL) 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. Patients should be well hydrated. Seizure-prone patients should be maintained on anticonvulsant medication.

Adverse Reactions

Any adverse reactions known to occur with the i.v. use of Optiray can also occur during myelography, especially those which originate in the CNS. 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 consequent dilution of contrast, injection should be made slowly, over 1 - 2 minutes.

Depending on the estimated volume of Optiray which 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, in the clinical judgment of the physician, a repeat examination is required, an interval of 5 days between procedures is recommended.

Usual Adult Dose:

The usual recommended total dose of Optiray 240 for use in lumbar myelography is 10 mL and for thoracic and cervical myelography 15 mL.

The following table indicates these dosages:

Procedure	Optiray Concentration	Concentration (mgI/mL)	Volume (mL)
Lumbar myelography	Optiray 240	240	10
Thoracic myelography	Optiray 240	240	15
Cervical myelography	Optiray 240	240	15

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

PATIENT MANAGEMENT - SUBARACHNOID ADMINISTRATION

Good patient management should be exercised at all times to minimize the potential for complications.

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.
- Raise head of stretcher to at least 30° before moving patient onto it.
- Movement onto and off the stretcher should be done slowly with patient completely passive, maintaining head up position.
- Before moving patient onto bed, raise head of bed 30° to 45°.

- Some clinicians advise patients to remain still in bed, in head up position or in the semi-sitting position, especially in the first few hours. Others have encouraged their patients to be fully ambulatory and have noted a reduction in the incidence of headache, nausea and vomiting.
- Maintain close observation and head-up position for at least 24 hours after myelogram.
- Obtain visitors' cooperation in keeping the patient quiet and in head up position, especially in first few hours.
- Encourage oral fluids. 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 replacement by intravenous fluids is recommended.

DOSAGE AND ADMINISTRATION

It is advisable that sterile Optiray products in vials, bottles or in Ultraject syringes be at or close to body temperature when infused.

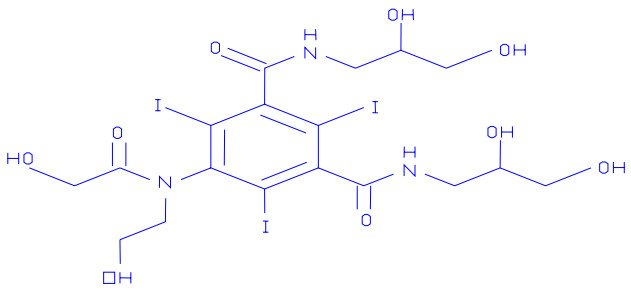
PHARMACEUTICAL INFORMATION

A. DRUG SUBSTANCE

Common Name: ioversol

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

Structural Formula:



Empirical Formula: $C_{18}H_{24}I_3N_3O_9$

Molecular Weight: 807.12

Description:

Appearance:	Ioversol is a fine, white, non-crystalline powder.
Solubility:	Ioversol is very soluble in water, freely soluble in dimethylformamide, sparingly soluble in ethanol, slightly soluble in acetone and very slightly soluble in acetonitrile.
Melting Point:	No melting point is observed.

B. COMPOSITION

Characteristics: 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.

Concentrations/mL: Optiray 160: each millilitre of Optiray 160 (ioversol injection 34%) provides 339 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. Optiray 160 provides 16% (160 mg/mL) of organically bound iodine.

Optiray 240: each millilitre of Optiray 240 (ioversol injection 34%) provides 339 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.

Optiray 300: each millilitre of Optiray 300 (ioversol injection 64%) 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.

Optiray 320: each millilitre of Optiray 320 (ioversol injection 68%) 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.

Optiray 350: each millilitre of Optiray 350 (ioversol injection 74%) 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.

Physical and Chemical Properties:

	OPTIRAY 160	OPTIRAY 240	OPTIRAY 300	OPTIRAY 320	OPTIRAY 350
Ioversol content (mg/mL)	339	509	636	678	741
Iodine content (mg/mL)	160	240	300	320	350
Osmolality (mOsm/kg)	355	502	651	702	792
Viscosity (cps)					
25°C	2.7	4.0	8.2	9.9	14.3
37°C	1.9	3.0	5.5	5.8	9.0

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

STABILITY AND STORAGE RECOMMENDATIONS

Recommendations

Store 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. Protect from freezing.

AVAILABILITY OF DOSAGE FORMS

OPTIRAY 160

Vials of 50 mL, boxes of 10 and 25
Bottles of 100 mL fill/150 mL, boxes of 6 and 12
Ultraject prefilled syringes 50/125 mL power injector and
125 mL power injector, boxes of 20

OPTIRAY 240

Vials of 15 mL fill/20 mL, boxes of 10 and 25
Vials of 50 mL, boxes of 10 and 25
Bottles of 55 mL fill/100 mL, boxes of 12
Bottles of 65 mL fill/l00 mL, boxes of 12
Bottles of 100 mL fill/l50 mL, boxes of 12
Bottles of 200 mL fill/250 mL, boxes of 12
Ultraject prefilled syringes 50 mL hand-held, 75 mL fill/125 mL power injector; 100 mL fill/125 mL power injector and 125 mL power injector, boxes of 20.

OPTIRAY 300

Vials of 30 mL, boxes of 25
Vials of 50 mL, boxes of 25
Bottles of 55 mL fill/100 mL, boxes of 12
Bottles of 65 mL fill/1 00 mL, boxes of 12
Bottles of 100 mL fill/150 mL, boxes of 12
Bottles of 150 mL, boxes of 12
Ultraject prefilled syringes 30 mL and 50 mL,
hand-held 50 mL fill/125 mL, power injector,
100 mL fill/125 mL power injector, 125 mL power injector, boxes of 20

OPTIRAY 320

Vials of 20 mL, boxes of 10 and 25
Vials of 30 mL, boxes of 10 and 25
Vials of 50 mL, boxes of 10 and 25
Bottles of 55 mL fill/100 mL, boxes of 12
Bottles of 65 mL fill/100 mL, boxes of 12
Bottles of 100 mL fill/150 mL, boxes of 12
Bottles of 150 mL, boxes of 12
Bottles of 200 mL fill/250 mL, boxes of 12
Ultraject prefilled syringes 30 mL and 50 mL hand-held,
50 mL fill/125 mL power injector, 75 mL fill/125 mL power injector; 100 mL fill/125 mL power injector; 125 mL power injector, boxes of 20.

OPTIRAY 350

Vials of 30 mL, boxes of 25
Vials of 50 mL, boxes of 25
Bottles of 75 mL fill/150 mL, boxes of 12
Bottles of 55 mL fill/100 mL, boxes of 12
Bottles of 65 mL fill/100 mL, boxes of 12
Bottles of 100 mL fill/150 mL, boxes of 12
Bottles of 150 mL, boxes of 12

Bottles of 200 mL fill/250 mL, boxes of 12
Ultraject prefilled syringes 30 and 50 mL hand-held; 50 mL fill/125 mL power injector; 75 mL fill/125 mL power injector; 100 mL fill/125 mL power injector; 125 mL power injector, boxes of 20.

PHARMACY BULK VIAL FOR OPTIRAY 320 and OPTIRAY 350 (500 mL BOTTLE)

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 or for use of diluted solution.

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.

ANIMAL PHARMACOLOGY

Distribution, Metabolism and Excretion

The biodistribution, metabolism and excretion of Optiray (Ioversol) were evaluated in rats and dogs following intravenous injection of 0.2 and 2,0 g I/kg, For these studies, Optiray (ioversol) 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 t1/2 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 t1/2 for ioverosl being 1.37 hr. and for iopamidol1.23 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 rout 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 (ioversol) 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 ($p<0.0I$) 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 effects, 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 grades 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: ioverol-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-l1.5 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 ioverol 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
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
Intracisternal	Sprague-Dawley rats: 67 f	5 rats per dose group Metrizamide; 60, 120, 240 Ioversol, iohexol and iopamidol: 240, 480, 720 7 saline controls	**Metrizamide rats**: hypoactivity pronounced and prolonged. Dose related fatalities: 1/5, 2/5 and 4/5 deaths at 60, 120 and 240 mgl/kg, respectively. All showed EEG abnormalities including abnormal slow wave activity, spike activity or both. **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. **Iohexol rats**: hypoactivity similar in magnitude to the saline controls, but slightly prolonged. Evident only at 480 & 720 mgl/kg. EEG patterns not different from saline controls except that 2 rats did not show normal alert patterns. **Ioversol rats**: similar changes to iohexol. Hypoactive for longer than saline controls. Few or no EEG abnormalities. At 480 mgI/kg, I 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. 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.

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 g/I/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 g/I/kg/day dose level in 4/8 dogs. They were not seen in dogs at the end of an 8 week recovery period.

15 DAY PLUS 4 WEEK SUBARACHNOID STUDY OF IOVERSOL 240 IN DOGS

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	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. 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. 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. Macroscopic examination revealed only a low incidence of hematoma at the injection site, comparable between treated and control animals. 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. 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.

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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, Escheriscia 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 effects were noted in the F_1 or F_2 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 effects on the dam or resulting litter parameters at 0.2 or 0.8 gI/kg/day; neither were there any adverse effects on the maturation of the F_1 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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