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Optiray® 350
[IOVERSOL INJECTION 74%]
Optiray® 320
[IOVERSOL INJECTION 68%]
Optiray® 300
[IOVERSOL INJECTION 64%]
Optiray® 240
[IOVERSOL INJECTION 51%]
Optiray® 160
[IOVERSOL INJECTION 34%]

tyco Healthcare/Mallinckrodt

Rx Only

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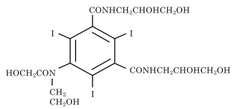
NOT FOR INTRATHECAL USE

DESCRIPTION

OPTIRAY (ioversol injection) formulations are sterile, nonpyrogenic, aqueous solutions intended for intravascular administration as diagnostic radiopaque media. Ioversol is designated chemically as *N,N'*-Bis (2,3-dihydroxypropyl)-5-[N-(2-hydroxyethyl) -glycolamido] -2,4,6-triiodoisophthalamide and has the following structural formula:



The molecular weight of ioversol is 807.11 and the organically bound iodine content is 47.2%. Ioversol is nonionic and does not dissociate in solution.

Each milliliter of OPTIRAY 350 (ioversol injection 74%) contains 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.

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

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

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

Each milliliter of OPTIRAY 160 (ioversol injection 34%) contains 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) organically bound iodine.

The pH of the OPTIRAY formulations has been adjusted to 6.0 to 7.4 with hydrochloric acid or sodium hydroxide. All solutions are sterilized by autoclaving and contain no preservatives. Unused portions should be discarded. OPTIRAY solutions are sensitive to light and therefore should be protected from exposure.

Some physical and chemical properties of these formulations are listed below:

	OPTIRAY 160	OPTIRAY 240	OPTIRAY 300	OPTIRAY 320	OPTIRAY 350
Ioversol content (mg/mL)	339	509	636	678	741
Iodine content (mg I/mL)	160	240	300	320	350
Osmolality (mOsm/kg water)	355	502	651	702	792
Viscosity (cps)					
at 25°C	2.7	4.6	8.2	9.9	14.3
at 37°C	1.9	3.0	5.5	5.8	9.0
Specific Gravity					
at 37°C	1.188	1.281	1.352	1.371	1.405

The OPTIRAY formulations are clear, colorless to pale yellow solutions containing no undissolved solids. Crystallization does not occur at room temperature. The products are supplied in containers from which the air has been displaced by nitrogen. OPTIRAY solutions have osmolalities 1.2 to 2.8 times that of plasma (285 mOsm/kg water) as shown in the above table and are hypertonic under conditions of use.

CLINICAL PHARMACOLOGY

The pharmacokinetics of ioversol intravascularly administered in normal 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.

Ioversol is excreted mainly through the kidneys following intravascular administration. In patients with impaired renal function, the elimination half-life is prolonged. In the absence of renal dysfunction, the mean half-life for urinary excretion following a 50 mL dose was 118 minutes (105 to 156) and following a 150 mL dose was 105 minutes (74 to 141). Greater than 95% of the administered dose was excreted within the first 24 hours, with the peak urine concentration occurring in the first 2 hours after administration. Fecal elimination was negligible.

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

OPTIRAY probably crosses the placental barrier in humans by simple diffusion. It is not known to what extent ioversol is excreted in human milk.

Intravascular injection of ioversol opacifies those vessels in the path of the flow of the contrast medium, permitting radiographic visualization of the internal structures until significant hemodilution occurs.

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

Animal studies indicate that ioversol does not cross the blood-brain barrier or cause endothelial damage to any significant extent.

OPTIRAY enhances computed tomographic imaging through augmentation of radiographic efficiency. The degree of density enhancement is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid intravenous injection. Blood levels fall rapidly within 5 to 10 minutes and the vascular compartment half-life is approximately 20 minutes. This can be accounted for by the dilution in the vascular and extravascular fluid compartments which causes an initial sharp fall in plasma concentration. Equilibration with the extracellular compartments is reached in about 10 minutes; thereafter, the fall becomes exponential.

The pharmacokinetics of ioversol in both normal and abnormal tissue have been shown to be variable. Contrast enhancement appears to be greatest immediately after bolus administration (15 seconds to 120 seconds). Thus, greatest enhancement may be detected by a series of consecutive two-to-three second scans performed within 30 to 90 seconds after injection (i.e., dynamic computed tomographic imaging). Utilization of a continuous scanning technique (i.e., dynamic CT scanning) may improve enhancement and diagnostic assessment of tumor and other lesions such as abscess, occasionally revealing unsuspected or more extensive disease. For example, a cyst may be distinguished from a vascularized solid lesion when precontrast and enhanced scans are compared; the nonperfused mass shows unchanged x-ray absorption (CT number). A vascularized lesion is characterized by an increase in CT number in the few minutes after a bolus of intravascular contrast agent; it may be malignant, benign, or normal tissue, but would probably not be a cyst, hematoma, or other nonvascular lesion.

Because unenhanced scanning may provide adequate diagnostic information in the individual patient, the decision to employ contrast enhancement, which may be associated with risk and increased radiation exposure, should be based upon a careful evaluation of clinical, other radiological, and unenhanced CT findings.

CT SCANNING OF THE HEAD

In contrast enhanced computed tomographic head imaging, OPTIRAY does not accumulate in normal brain tissue due to the presence of the normal blood-brain barrier. The increase in x-ray absorption in the normal brain is due to the presence of contrast agent within the blood pool. A break in the blood-brain barrier such as occurs in malignant tumors of the brain allows for the accumulation of contrast medium within the interstitial tissue of the tumor. Adjacent normal brain tissue does not contain the contrast medium.

Maximum contrast enhancement in tissue frequently occurs after peak blood iodine levels are reached. A delay in maximum contrast enhancement can occur. Diagnostic contrast enhanced images of the brain have been obtained up to 1 hour after intravenous bolus administration. This delay suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine containing medium within the lesion and outside the blood pool, although the mechanism by which this occurs is not clear. The radiographic enhancement of nontumoral lesions, such as arteriovenous malformations and aneurysms, is probably dependent on the iodine content of the circulating blood pool.

In patients where the blood-brain barrier is known or suspected to be disrupted, the use of any radiographic contrast medium must be assessed on an individual risk to benefit basis. However, compared to ionic media, nonionic media are less toxic to the central nervous system.

CT SCANNING OF THE BODY

In contrast enhanced computed tomographic body imaging (nonneural tissue), OPTIRAY diffuses rapidly from the vascular into the extravascular 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 of tumors since no barrier exists. Contrast enhancement is thus due to the relative differences in extravascular diffusion between normal and abnormal tissue, quite different from that in the brain.

INDICATIONS AND USAGE

OPTIRAY 350 is indicated in adults for peripheral and coronary arteriography and left ventriculography. OPTIRAY 350 is also indicated for contrast enhanced computed tomographic imaging of the head and body, intravenous excretory urography, intravenous digital subtraction angiography and venography. OPTIRAY 350 is indicated in children for angiocardiography.

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

OPTIRAY 320 is indicated in children for angiocardiography, contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography.

OPTIRAY 300 is indicated for cerebral angiography and peripheral arteriography. OPTIRAY 300 is also indicated for contrast enhanced computed tomographic imaging of the head and body, venography, and intravenous excretory urography.

OPTIRAY 240 is indicated for cerebral angiography and venography. OPTIRAY 240 is also indicated for contrast enhanced computed tomographic imaging of the head and body and intravenous excretory urography.

OPTIRAY 160 is indicated for intra-arterial digital subtraction angiography (IA-DSA).

CONTRAINDICATIONS

None.

WARNINGS

SEVERE ADVERSE EVENTS — INADVERTENT INTRATHECAL ADMINISTRATION: Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not administered intrathecally.

Nonionic iodinated contrast media inhibit blood coagulation, *in vitro*, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, 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 guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

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

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium has not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication to the procedure; however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiopaque materials to patients known or suspected of having 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 procedures may be performed; however, 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.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

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

PRECAUTIONS

General

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

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

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See Adverse Reactions). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

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

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

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Information for Patients

Patients receiving iodinated intravascular contrast agents should be instructed to:

1. Inform your physician if you are pregnant.
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease or known thyroid disorder. (See WARNINGS).
3. Inform your physician if you are allergic to any drugs or food, or if you had any reactions to previous injections of dyes used for x-ray procedures. (See PRECAUTIONS, General).
4. Inform your physician about any other medications you are currently taking including non-prescription drugs.

Drug Interactions

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

Other drugs should not be mixed with ioversol injection.

Drug / Laboratory Test Interactions

The results of PBI and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Category B

No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier or reaches fetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter fetal tissue passively. Because animal teratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in children have been established for the use of OPTIRAY 350 and OPTIRAY 320 in angiocardiography, and for OPTIRAY 320 in contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography.

Safety and effectiveness in newborns have not been established.

ADVERSE REACTIONS

Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media.

Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY was used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemodynamic changes occurred with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium.

Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) than with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude, ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressure, right ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures.

The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in 2,098 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system regardless of frequency.

Adverse Reactions

System	>1%	≤1%
Cardiovascular	none	angina pectoris hypotension blood pressure fluctuation arterial spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	nausea(1.2)	vomiting dry mouth
Nervous	headache(1.1)	cerebral infarct blurred vision vertigo lightheadedness visual hallucination vasovagal reaction disorientation paresthesia dysphasia muscle spasm syncope
Respiratory	none	laryngeal edema pulmonary edema sneezing congestion coughing shortness of breath hypoxia
Skin	none	periorbital edema urticaria pruritus facial edema flush erythema

Adverse Reactions, continued

System	>1%	≤1%
Miscellaneous	none	extravasation hematoma shaking chills bad taste general pain renal colic fever polyuria urinary retention

Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

Pediatrics

In controlled clinical trials involving 159 patients for pediatric angiocardiography, contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography, adverse reactions reported were as follows: fever (1.3%), nausea (0.6%), muscle spasm (0.6%), LV pressure changes (0.6%).

General Adverse Reactions to Contrast Media

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

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. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physiochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated contrast agent.

Nervous: convulsions, aphasia, paralysis, visual field losses which are usually transient but may be permanent, coma and death.

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy.

Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

(Adverse reactions for specific procedures receive comment in the Indications, Usage and Procedural Information section).

OVERDOSAGE

The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Ioversol does not bind to plasma or serum protein and is, therefore, dialyzable.

The intravenous LD_{50} values (gI/kg) for ioversol in animals were: 17 (mice), and 15 (rats).

DOSAGE AND ADMINISTRATION

General

As with all radiopaque contrast agents, only the lowest dose necessary to obtain adequate visualization should be used. A lower dose may reduce the possibility of an adverse reaction. Most procedures do not require use of either the maximum volume or the highest concentration of OPTIRAY. The

combination of volume and concentration of OPTIRAY to be used should be carefully individualized accounting for factors such as age, body weight, size of the vessel and the rate of blood flow within the vessel. Other factors such as anticipated pathology, degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed should be considered.

It is desirable that intravascularly administered iodinated contrast agents be at or close to body temperature when injected.

If during administration a reaction occurs, the injection should be stopped until the reaction has subsided.

Patients should be well hydrated prior to and following OPTIRAY (ioversol injection) administration.

As with all contrast media, other drugs should not be mixed with ioversol solutions because of the potential for chemical incompatibility.

Sterile technique must be used in all vascular injections involving contrast media.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Withdrawal of contrast agents from their containers should be accomplished under strict aseptic conditions using only sterile syringes and transfer devices. Contrast agents which have been transferred into other delivery systems should be used immediately.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and should not be used if particulates are observed or marked discoloration has occurred.

The OPTIRAY formulations are supplied in single dose containers. Discard unused portion.

INDIVIDUAL INDICATIONS, USAGE AND PROCEDURAL INFORMATION

GENERAL ANGIOGRAPHY

Visualization of the cardiovascular system may be accomplished by any accepted radiological technique. Since intra-arterial digital subtraction angiography (IA-DSA) requires adjustments in the method of administration, this procedure is described separately.

Cerebral Arteriography

Additional Precautions and Adverse Reactions: Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine. Cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are: seizures, drowsiness, transient paresis, and mild disturbances in vision.

Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that were considered drug-related and occurred with frequencies greater than 1% were: headache, bradycardia, blood pressure fluctuation, disorientation, nausea and vertigo.

Dosage and Administration: OPTIRAY 240, OPTIRAY 300 or OPTIRAY 320 is recommended for this procedure. The usual individual injection for visualization of the carotid or vertebral arteries is 2 to 12 mL, repeated as necessary. Aortic arch injection for a simultaneous four vessel study requires 20 to 50 mL. Total procedural doses should not usually exceed 200 mL.

Peripheral Arteriography

Additional Precautions: Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Dosage and Administration: OPTIRAY 300, OPTIRAY 320 or OPTIRAY 350 is recommended for this procedure. The usual individual injection volumes for visualization of various peripheral arteries are as follows:

aorta-iliac runoff	—	60 mL (range 20 to 90 mL)
common iliac, femoral	—	40 mL (range 10 to 50 mL)
subclavian, brachial	—	20 mL (range 15 to 30 mL)

These doses may be repeated as necessary. Total procedural doses should not usually exceed 250 mL.

Visceral and Renal Arteriography and Aortography

Additional Precautions and Adverse Effects: In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, retroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transverse myelitis.

Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows.

Dosage and Administration: OPTIRAY 320 is recommended for visceral arteriography, renal arteriography, and aortography procedures. The usual individual injection volumes for visualization for the aorta and various visceral arteries are as follows:

aorta	—	45 mL (range 10 to 80 mL)
celiac	—	45 mL (range 12 to 60 mL)
superior mesenteric	—	45 mL (range 15 to 60 mL)
renal or inferior mesenteric	—	9 mL (range 6 to 15 mL)

These doses may be repeated as necessary. Total procedural doses should not usually exceed 250 mL.

Coronary Arteriography and Left Ventriculography

Additional Precautions: Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure.

Adverse Reactions: There were no cardiovascular system reactions with OPTIRAY in controlled clinical studies in coronary arteriography with left ventriculography that were considered drug-related and occurred with a frequency greater than 1%.

Dosage and Administration: OPTIRAY 320 or OPTIRAY 350 is recommended for this procedure. The usual individual injection volumes for visualization of the coronary arteries and left ventricle are:

left coronary	—	8 mL (range 2 to 10 mL)
right coronary	—	6 mL (range 1 to 10 mL)
left ventricle	—	40 mL (range 30 to 50 mL)

These doses may be repeated as necessary. Total procedural dose for the combined procedures should not usually exceed 250 mL. When large individual volumes are administered, as in ventriculography and aortography, it has been suggested that several minutes be permitted to elapse between each injection to allow for subsidence of possible hemodynamic disturbances.

Pediatric Angiocardiography

Additional Precautions: Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure. Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL, or those less than 12 months of age.

Dosage and Administration: OPTIRAY 350 or OPTIRAY 320 is recommended for this procedure. The usual single ventricular injection of OPTIRAY 350 or OPTIRAY 320 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.

Intra-arterial Digital Subtraction Angiography (IA-DSA)

All of the arteriographic procedures described above can be performed using digital subtraction techniques.

Dosage and Administration: OPTIRAY 160 is recommended for this procedure. As a general rule, the volume and concentration used for IA-DSA is 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 only as a guide. Injections may be repeated as necessary. It is advisable to inject at rates approximately equal to the flow of the vessel being injected.

Carotid Arteries	6 to 10 mL
Vertebral Arteries	4 to 8 mL
Aorta	25 to 50 mL
Subclavian or Brachial Arteries	2 to 10 mL
Major Branches of the Abdominal Aorta	2 to 20 mL

Dosage should not usually exceed 250 mL.

Venography

Additional Precautions: Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In order to minimize extravasation during injection, fluoroscopy is recommended.

Dosage and Administration: OPTIRAY 240, OPTIRAY 300, OPTIRAY 320 or OPTIRAY 350 is recommended for this procedure. The usual dose is 50 to 100 mL per extremity with smaller or larger volumes indicated in some cases. Dosage should not usually exceed 250 mL.

Following the procedure, the venous system should be flushed with Sodium Chloride Injection U.S.P. or 5% Dextrose in Water (D5W). Massage and elevation are also helpful for clearing the contrast medium from the extremity.

COMPUTED TOMOGRAPHY

OPTIRAY 350, OPTIRAY 320, OPTIRAY 300 or OPTIRAY 240 is recommended for head imaging.

OPTIRAY 350, OPTIRAY 320, OPTIRAY 300 or OPTIRAY 240 is recommended for body imaging.

Head Imaging

Tumors: OPTIRAY may be useful to investigate the presence and extent of certain malignancies such as: gliomas including malignant gliomas, glioblastomas, astrocytomas, oligodendrogliomas and gangliomas, ependymomas, medulloblastomas, meningiomas, neuromas, pinealomas, pituitary adenomas, craniopharyngiomas, germinomas, and metastatic lesions. 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 calcified lesions, there is less likelihood of enhancement. Following therapy, tumors may show decreased or no

enhancement. The opacification of the inferior vermis following contrast media administration has resulted in false-positive diagnosis in a number of otherwise normal studies.

Nonneoplastic Conditions: OPTIRAY may be beneficial in the image enhancement of nonneoplastic lesions. Cerebral infarctions of recent onset may be better visualized with contrast enhancement, while some infarctions are obscured if contrast medium is used. The use of iodinated contrast media results in enhancement in about 60% of cerebral infarctions studied from one to four weeks from the onset of symptoms.

Sites of active infection may also be enhanced following contrast medium administration.

Arteriovenous malformations and aneurysms will show contrast enhancement. For these vascular lesions the enhancement is probably dependent on the iodine content of the circulating blood pool. Hematomas and intraparenchymal bleeders seldom demonstrate contrast enhancement. However, in cases of intraparenchymal clot, for which there is no obvious clinical explanation, contrast media administration may be helpful in ruling out the possibility of associated arteriovenous malformation.

Dosage and Administration: Adults: For adults, the usual dosage is 50 to 150 mL of OPTIRAY 350, OPTIRAY 320 or OPTIRAY 300 or 100 to 250 mL of OPTIRAY 240. Scanning may be performed immediately after completion of the intravenous administration. Dosage should not usually exceed 150 mL of OPTIRAY 350, OPTIRAY 320 or OPTIRAY 300 or 250 mL of OPTIRAY 240.

Children: The dosage recommended for use in children is 1 mL/kg to 3 mL/kg of OPTIRAY 320.

Body Imaging

OPTIRAY may be useful for enhancement of computed tomographic images for detection and evaluation of lesions in the liver, pancreas, kidneys, aorta, mediastinum, pelvis, abdominal cavity, and retroperitoneal space.

Enhancement of computed tomography with OPTIRAY may be of benefit in establishing diagnoses of certain lesions in these sites with greater assurance than is possible with CT alone. In other cases, the contrast agent may allow visualization of lesions not seen with CT alone (i.e., tumor extension) or may help to define suspicious lesions seen with unenhanced CT (i.e., pancreatic cyst).

Dosage and Administration: Adults: OPTIRAY 350, OPTIRAY 320, OPTIRAY 300 or OPTIRAY 240 may be administered by bolus injection, by rapid infusion, or by a combination of both. The usual doses are summarized below:

	bolus injection	infusion
OPTIRAY 350	25 to 75 mL	50 to 150 mL
OPTIRAY 320	25 to 75 mL	50 to 150 mL
OPTIRAY 300	25 to 75 mL	50 to 150 mL
OPTIRAY 240	35 to 100 mL	70 to 200 mL

Dosage should not usually exceed 150 mL of OPTIRAY 350, OPTIRAY 320 or OPTIRAY 300 or 250 mL of OPTIRAY 240.

Children: The dosage recommended for use in children is 1 mL/kg to 3 mL/kg of OPTIRAY 320, with a usual dose of 2 mL/kg.

INTRAVENOUS DIGITAL SUBTRACTION ANGIOGRAPHY

Intravenous digital subtraction angiography (IV DSA) is a radiographic modality which allows dynamic imaging of the arterial system following intravenous injection of iodinated x-ray contrast media through the use of image intensification, enhancement of the iodine signal and digital processing of the image data. Temporal subtraction of the images obtained prior to and during the "first arterial pass" of the injected contrast medium yields images which are devoid of bone and soft tissue.

IV DSA is most frequently used to examine the heart, including coronary by-pass grafts; the pulmonary arteries; arteries of the brachiocephalic circulation; the aortic arch; the abdominal aorta and its major branches; the iliac arteries; and the arteries of the extremities.

Patient Preparation

No special patient preparation is required for IV DSA. However, it is advisable to insure that patients are well hydrated prior to examination.

Precautions

In addition to the general precautions previously described, the risks associated with IV DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Usual Dosage

OPTIRAY 350 may be injected centrally, in either the superior or inferior vena cava or right atrium; or peripherally into an appropriate arm vein. For central injections, catheters may be introduced at the antecubital fossa into either the basilic or cephalic vein or at the leg into the femoral vein and advanced to the distal segment of the corresponding vena cava. For peripheral injections, the catheter is introduced at the antecubital fossa into an appropriate size arm vein. In order to reduce the potential for extravasation during peripheral injection, a catheter of approximately 20 cm in length should be employed.

Depending on the area to be imaged, the usual dose range per injection is 30 to 50 mL. Injections may be repeated as necessary. The total procedural dose should not exceed 250 mL.

Injection rates will vary depending on the site of catheter placement and vessel size. Central catheter injections are usually made at a rate of between

10 and 30 mL/second. Peripheral injections are usually made at a rate of between 12 and 20 mL/second. Since the injected medium can sometimes remain in the arm vein for an extended period, it is advisable to flush the vein immediately following injection with an appropriate volume (20 to 25 mL) of Sodium Chloride Injection U.S.P. or 5% Dextrose in Water (D5W).

INTRAVENOUS UROGRAPHY

Dosage and Administration: OPTIRAY 350, OPTIRAY 320, OPTIRAY 300 or OPTIRAY 240 is recommended for routine and high dose excretory urography. Preparatory dehydration is dangerous and may contribute to acute renal failure (see PRECAUTIONS, General).

Adults: The usual dose for routine excretory urography in adults is 50 to 75 mL of OPTIRAY 350, OPTIRAY 320 or OPTIRAY 300 or 75 to 100 mL of OPTIRAY 240. Higher dosages may be indicated to achieve optimum results where poor visualization is anticipated (e.g., elderly patients or patients with impaired renal function). In these patients, high dose urography may be preferred, using OPTIRAY 350 at a dose of 1.4 mL/kg (maximum 140 mL), OPTIRAY 320 at a dose of 1.5 to 2 mL/kg (maximum 150 mL), OPTIRAY 300 at a dose of 1.6 mL/kg (maximum 150 mL) or OPTIRAY 240 at a dose of 2 mL/kg (maximum 200 mL).

Children: OPTIRAY 320 at doses of 0.5 mL/kg to 3 mL/kg of body weight has produced diagnostic opacification of the excretory tract. The usual dose for children is 1 mL/kg to 1.5 mL/kg. Dosage for infants and children should be administered in proportion to age and body weight. The total administered dose should not exceed 3 mL/kg.

HOW SUPPLIED

OPTIRAY 350	**NDC Number**
Glass	
25x50 mL bottles	0019-1333-06
12x75 mL fill/100 mL bottles	0019-1333-41
12x100 mL bottles	0019-1333-11
12x150 mL bottles	0019-1333-16
12x200 mL fill/250 mL bottles	0019-1333-21
Plastic	
20x30 mL hand held syringes	0019-1333-73
20x50 mL hand held syringes	0019-1333-75
20x50 mL fill/125 mL power injector syringes	0019-1333-77
20x75 mL fill/125 mL power injector syringes	0019-1333-91
20x100 mL fill/125 mL power injector syringes	0019-1333-83
20x125 mL power injector syringes	0019-1333-81
Plastic (OptiVantage)	
20x50 mL fill/125 mL power injector syringes	0019-1333-50
20x75 mL fill/125 mL power injector syringes	0019-1333-07
20x100 mL fill/125 mL power injector syringes	0019-1333-10
20x125 mL power injector syringes	0019-1333-25

OPTIRAY 320	
Glass	
25x20 mL vials	0019-1323-02
25x30 mL vials	0019-1323-04
25x50 mL bottles	0019-1323-06
12x75 mL fill/100 mL bottles	0019-1323-41
12x100 mL bottles	0019-1323-11
12x150 mL bottles	0019-1323-16
12x200 mL fill/250 mL bottles	0019-1323-21
Plastic	
20x30 mL hand held syringes	0019-1323-73
20x50 mL hand held syringes	0019-1323-75
20x50 mL fill/125 mL power injector syringes	0019-1323-77
20x75 mL fill/125 mL power injector syringes	0019-1323-91
20x100 mL fill/125 mL power injector syringes	0019-1323-83
20x125 mL power injector syringes	0019-1323-81
Plastic (OptiVantage)	
20x50 mL fill/125 mL power injector syringes	0019-1323-50
20x75 mL fill/125 mL power injector syringes	0019-1323-07
20x100 mL fill/125 mL power injector syringes	0019-1323-10
20x125 mL power injector syringes	0019-1323-25

OPTIRAY 300	
Glass	
25x50 mL bottles	0019-1332-06
12x100 mL bottles	0019-1332-11
12x150 mL bottles	0019-1332-16
12x200 mL fill/250 mL bottles	0019-1332-21
Plastic	
20x50 mL hand held syringes	0019-1332-75
20x100 mL fill/125 mL power injector syringes	0019-1332-83
20x125 mL power injector syringes	0019-1332-81
Plastic (OptiVantage)	
20x100 mL fill/125 mL power injector syringes	0019-1332-10

OPTIRAY 240	
Glass	
25x50 mL bottles	0019-1324-06
12x100 mL bottles	0019-1324-11
12x150 mL bottles	0019-1324-16
12x200 mL fill/250 mL bottles	0019-1324-21
Plastic	
20x50 mL hand held syringes	0019-1324-75
20x125 mL power injector syringes	0019-1324-81
Plastic (OptiVantage)	
20x125 mL power injector syringes	0019-1324-25

OPTIRAY 160	**NDC Number**
Glass	
25x50 mL bottles	0019-1325-06
12x100 mL bottles	0019-1325-11

Storage: Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. These products are sensitive to light and must be protected from strong daylight or direct exposure to the sun. If product is frozen or if crystallization occurs, examine the container for physical damage. If no damage has occurred, the container should be brought to room temperature. Shake vigorously to assure complete dissolution of any crystals. The speed of dissolution may be increased by heating with circulating warm air. Submersion of syringes in water is not recommended. OPTIRAY may be stored at 37°C for up to one month in a contrast media warmer utilizing circulating warm air. For periods longer than one month, store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Before use, examine the product to assure that all solids are redissolved. Do not reautoclave plastic container because of possible damage to syringe.

As with all contrast media, glass and plastic containers should be inspected prior to use to ensure that breakage or other damage has not occurred during shipping and handling. All containers should be inspected for closure integrity. Damaged containers should not be used.

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