

March 2017

Optiray® Pharmacy Bulk Package - 350
[Ioversol Injection 74%]

Optiray® Pharmacy Bulk Package - 320
[Ioversol Injection 68%]

Optiray® Pharmacy Bulk Package - 300
[Ioversol Injection 64%]

Rx only

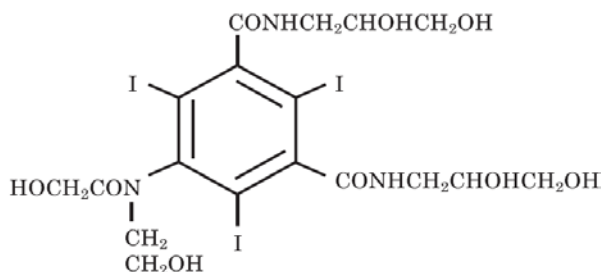
Pharmacy Bulk Package - Not for Direct Infusion

WARNING
NOT FOR INTRATHECAL USE

DESCRIPTION

Optiray (ioversol injection) formulations are sterile, nonpyrogenic, aqueous solutions intended for intravascular administration as diagnostic radiopaque media. Each bottle is to be used as a Pharmacy Bulk Package for dispensing multiple single dose preparations utilizing a suitable transfer device.

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 Pharmacy Bulk Package - 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 Pharmacy Bulk Package - 350 provides 35% (350 mg/mL) organically bound iodine.

Each milliliter of Optiray Pharmacy Bulk Package - 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 Pharmacy Bulk Package - 320 provides 32% (320 mg/mL) organically bound iodine.

Each milliliter of Optiray Pharmacy Bulk Package - 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 Pharmacy Bulk Package - 300 provides 30% (300 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 300	Optiray 320	Optiray 350
Ioversol content (mg/mL)	636	678	741
Iodine content (mg I/mL)	300	320	350
Osmolality (mOsm/kg water)	651	702	792
Viscosity (cps) at 25°C	8.2	9.9	14.3
at 37°C	5.5	5.8	9.0
Specific Gravity at 37°C	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 2.3 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 angiocardiology.

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 angiocardiology, 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.

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 ensure 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.

Severe Cutaneous Adverse Reactions: Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agent; prophylactic medications may not prevent or mitigate severe cutaneous adverse

reactions. Avoid administering Optiray to patients with a history of a severe cutaneous adverse reaction to Optiray.

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 non-diabetic 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 ensure 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 angiocardiology 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.
5. Advise patients to inform their physician if they develop a rash after receiving Optiray.

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 angiocardiology, 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. However, serious, life-threatening and fatal reactions have been associated with the administration of Optiray. Optiray has also been shown to cause changes in cardiac function and systemic blood pressure. These changes 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 4,187 patients. This listing includes reactions associated with the administration of ioversol. Adverse reactions are listed by organ system according to clinical importance. More severe reactions are listed before others in a system regardless of frequency. The most common reaction is nausea, occurring at a rate of greater than 1 percent. All other reactions in the table occur at less than 1 percent.

Adverse Reactions

System	Adverse Reactions
Cardiac disorders	Cardiac arrest Myocardial infarction Arrhythmia Atrioventricular block complete Atrioventricular block Nodal rhythm Bradycardia Angina pectoris Palpitations
Ear and labyrinth disorders	Vertigo Tinnitus
Eye disorders	Vision blurred Periorbital edema Conjunctivitis
Gastrointestinal disorders	Vomiting Abdominal pain Dysphagia Dry mouth
General disorders and administration site conditions	Chest Pain Pain Injection Site Pain Injection Site Hematoma Extravasation Pyrexia Swelling Asthenia Malaise Fatigue Chills
Infections and infestations	Rhinitis
Injury, poisoning, and procedural complications	Heart injury Vascular pseudoaneurysm
Investigations	Electrocardiogram ST segment

	depression Blood pressure decreased
Metabolism and nutrition disorders	Acidosis
Musculoskeletal and connective tissue disorders	Muscular weakness Muscle spasms Back Pain
Nervous system disorders	Cerebral infarction Aphasia Tremor Dizziness Presyncope Headache Paraesthesia Dysgeusia
Psychiatric disorders	Hallucination, visual Hallucination Disorientation Anxiety
Renal and urinary disorders	Urinary retention Renal Pain Polyuria
Respiratory, thoracic, and mediastinal disorders	Laryngeal edema Hypoxia Pulmonary edema Dyspnea Hyperventilation Cough Sneezing Nasal congestion
Skin and subcutaneous tissue disorders	Urticaria Rash Pruritus Swelling face Hyperhidrosis Erythema
Vascular disorders	Hypertension Hypotension Arterial spasm Vasospasm Vasodilation Flushing

Pediatrics

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

Postmarketing Experience

The following adverse drug reactions have been reported during post-approval use of Optiray. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency.

Endocrine disorders: transient hypothyroidism neonatal

Eye disorders: transient cortical blindness

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

Immune system disorders: anaphylactoid shock (with multi-organ failure and cardio-respiratory arrest which may be fatal), anaphylactic shock, anaphylactic/hypersensitivity reaction, urticaria

Renal and urinary disorders: acute kidney injury

Skin and subcutaneous tissue disorders: erythema multiforma, acute generalized exanthematous pustulosis (AGEP)

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 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.

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

Skin and Subcutaneous Tissue Disorders: Reactions range from mild (e.g. rash, erythema, pruritus, urticaria and skin discoloration) to severe: [e.g. Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)].

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 LD₅₀ values (g/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.

INDIVIDUAL INDICATIONS, USAGE AND PROCEDURAL INFORMATION

GENERAL ANGIOGRAPHY

Visualization of the cardiovascular system may be accomplished by any accepted radiological technique.

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 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.

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 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 USP 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 or Optiray 300 is recommended for head imaging.

Optiray 350, Optiray 320 or Optiray 300 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.

Non-neoplastic Conditions

Optiray may be beneficial in the image enhancement of non-neoplastic 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. 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.

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 or Optiray 300 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

Dosage should not usually exceed 150 mL of Optiray 350, Optiray 320 or Optiray 300.

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 ensure 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 ensure 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 USP or 5% Dextrose in Water (D5W).

INTRAVENOUS UROGRAPHY

Dosage and Administration

Optiray 350, Optiray 320 or Optiray 300 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. 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), or Optiray 300 at a dose of 1.6 mL/kg (maximum 150 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.

DRUG HANDLING OPTIRAY, PHARMACY BULK PACKAGE

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

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.

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

Directions for Proper Use of Optiray, Pharmacy Bulk Package

1. The container closure may be penetrated only one time, utilizing a suitable sterile transfer device or dispensing set which allows measured distribution of the contents.
2. The transferring of Optiray from the Pharmacy Bulk Package is restricted to a suitable work area, such as a laminar flow hood, utilizing aseptic technique.
3. The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of 4 hours from initial closure entry is permitted to complete fluid transfer operations.
4. Temperature of container after the closure has been entered should not exceed 25°C (77°F).

HOW SUPPLIED

	NDC Number
Optiray Pharmacy Bulk Package - 350 6x500 mL Pharmacy Bulk Packages	0019-1333-61
Optiray Pharmacy Bulk Package - 320 6x500 mL Pharmacy Bulk Packages	0019-1323-61
Optiray Pharmacy Bulk Package - 300 6x500 mL Pharmacy Bulk Packages	0019-1332-61

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, the bottle and contents should be discarded.

The transferring of Optiray from the Optiray Pharmacy Bulk Package should be performed in a suitable work area, such as a laminar flow hood, utilizing aseptic technique. The container closure may be penetrated only one time, utilizing a suitable transfer device. The withdrawal of container contents should be accomplished without delay. However, if this is not possible, a maximum time of 4 hours from initial closure entry is permitted to complete fluid transfer operations. Temperature of container after the closure has been entered should not exceed 25°C (77°F).

As with all contrast media, glass 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.

Manufactured by:
Liebel-Flarsheim Company LLC
Raleigh, NC 27616

Made in USA

GBT 13PB0317
Revised 03/17

Guerbet | 