GE Healthcare

VISIPAQUE™ (iodixanol) Injection

270 320

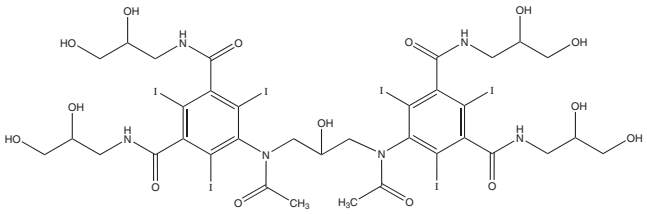
NOT FOR INTRATHECAL USE

Rx ONLY

DESCRIPTION

VISIPAQUE™ (iodixanol) Injection, 5,5´-[(2-hydroxy-1,3-propanediyl)bis (acetylimino)] bis[N,N´-bis(2,3-dihydroxypropyl)-2,4,6- triiodo-1,3- benzenedicarboxamide], is a dimeric, isosmolar, nonionic, water-soluble, radiographic contrast medium with a molecular weight of 1550.20 (iodine content 49.1%). It is administered by intravascular injection.

VISIPAQUE ($C_{35}H_{44}I_6N_6O_{15}$) has the following chemical structure:



VISIPAQUE Injection is provided as a ready-to-use sterile, pyrogen-free, colorless to pale yellow solution, in concentrations of 270 and 320 mg of organically bound iodine per mL (550 and 652 mg of iodixanol per mL, respectively). Sodium chloride and calcium chloride have been added, resulting in an isotonic solution for injection. VISIPAQUE 270 (270 mgI/mL) contains 0.074 mg calcium chloride dihydrate per mL and 1.87 mg sodium chloride per mL, and VISIPAQUE 320 (320 mgI/mL) contains 0.044 mg calcium chloride dihydrate per mL and 1.11 mg sodium chloride per mL, providing for both concentrations a sodium/calcium ratio equivalent to blood. In addition, each milliliter contains 1.2 mg tromethamine and 0.1 mg edetate calcium disodium. The pH is adjusted to 7.4 with hydrochloric acid and/or sodium hydroxide to achieve a range between pH 6.8 and 7.7 at 22°C. All solutions are terminally sterilized by autoclaving and contain no preservatives.

The two concentrations of VISIPAQUE Injection (270 mgI/mL and 320 mgI/mL) have the following physical properties:

PHYSICAL PROPERTIES of VISIPAQUE

Parameter		Concentration (mgI/mL)	
		320	270
Osmolality (mOsmol/kg water)		290	
Viscosity (cP)	@ 20°C	26.6	12.7
	@ 37°C	11.8	6.3
Density (g/mL)	@ 20°C	1.369	1.314
	@ 37°C	1.356	1.303

CLINICAL PHARMACOLOGY

GENERAL

Iodixanol is a dimeric, isosmolar, nonionic, water soluble, iodinated x-ray contrast agent for intravascular administration.

Intravascular injection of iodixanol opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

PHARMACOKINETICS

Distribution: In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution was 0.26 L/kg body weight, consistent with distribution to extracellular space.

Metabolism: Iodixanol metabolites have not been demonstrated.

Excretion: Plasma and urine levels suggest that body clearance of iodixanol is primarily due to renal clearance. In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within five days post-injection. In 40 healthy, young male volunteers receiving a single intravenous administration of VISIPAQUE Injection in doses of 0.3 to 1.2 gI/kg body weight, the elimination half-life was 2.1 hr (± 0.1); and renal clearance was 110 mL/min (±14), equivalent to glomerular filtration (108 mL/min). These values were independent of the dose administered.

Special Populations:

Pediatric: Forty pediatric patients ≤12 years old, with renal function that is normal for their age, received multiple intra-arterial administrations of VISIPAQUE Injection in doses of 0.32 to 3.2 gI/kg body weight. The elimination half-lives for these patients are shown in the following table and are derived from the mean terminal elimination rate constants (K_{el}): 0.185 hr^{-1} (newborn to 2 months old), 0.256 hr^{-1} (2 to <6 months old), 0.299 hr^{-1} (6 months to <1 year), 0.322 hr^{-1} (1 to <2 years), and 0.307 hr^{-1} (2 to ≤12 years old). The adult mean terminal elimination rate constant is 0.336 hr^{-1}. The actual VISIPAQUE clearance and volume of distribution in pediatric patients were not determined. Pharmacodynamic dose adjustments to account for differences in elimination half-life in pediatric patients under 6 months of age have not been studied. (For pediatric dosing see the Dosage and Administration section; for age adjusted adverse events see the Pediatric Use section).

MEAN ELIMINATION HALF-LIFE* IN PEDIATRIC PATIENTS

Age Range	Number of Patients	Elimination half-life
		(hr ± SD)
Newborn - < 2 months	8	4.1 ± 1.4
2 - 6 months	8	2.8 ± 0.6
6 - 12 months	9	2.4 ± 0.4
1 - 2 years	5	2.3 ± 0.6
2 - 12 years	10	2.3 ± 0.5
Adults	40	2.1 ± 0.1

* Calculated from the elimination rate constant. Actual clearance and volume of distribution were not measured.

Renal Insufficiency: In patients with significantly impaired renal function, the total clearance of iodixanol is reduced and the half-life in plasma phase is prolonged. In a study of 16 adult patients who were scheduled for renal transplant, the elimination of iodixanol 320 mgI/mL was studied. The patients' baseline mean creatinine levels were 6.3 mg/dL (±1.5) and mean creatinine clearances were 13.61 mL/min (±4.67). In these patients, the plasma half-life was increased to 23 hours (normal $t_{1/2}$ = 2 hours). In these patients, levels of iodixanol were detected 5 days after dosing. Contrast enhancement time in kidneys increased from 6 hours to at least 24 hours. Dose adjustments in patients with renal impairment have not been studied. (See PHARMACODYNAMICS section for renal failure and blood-brain barrier interactions.)

VISIPAQUE has been shown to be dialyzable. In an *in vitro* hemodialysis study, after 4 hours of dialysis with a cellulose membrane, approximately 36% of iodixanol was removed from the plasma. After 4 hours of dialysis with polysulfone membranes, approximately 49% of iodixanol was removed.

Drug-Drug Interactions: Not known.

PHARMACODYNAMICS

As with other iodinated contrast agents, following administration of VISIPAQUE Injection, the degree of enhancement is directly related to the iodine content in an administered dose; peak iodine plasma levels occur immediately following rapid intravascular injection. Iodine plasma levels fall rapidly within 5 to 10 minutes. This can be accounted for by the dilution in the vascular and extravascular fluid compartments.

Intravascular Contrast: Contrast enhancement with iodinated contrast agents appears to be greatest immediately after bolus injections (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).

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

Contrast Enhanced Computerized Tomography (CECT): AS WITH OTHER IODINATED CONTRAST AGENTS, THE USE OF VISIPAQUE INJECTION CONTRAST ENHANCEMENT MAY OBSCURE SOME LESIONS WHICH WERE SEEN ON PREVIOUSLY UNENHANCED CT SCANS.

In CECT some performance characteristics are different in the brain and body. In CECT of the body, iodinated contrast agents diffuse rapidly from the vascular into the extravascular space. Following the administration of iodinated contrast agents, the increase in tissue density to x-rays is related to blood flow, the concentration of the contrast agent, and the extraction of the contrast agent by various interstitial tissues. Contrast enhancement is thus due to relative differences in extravascular diffusion between adjacent tissues.

In normal brain with an intact blood-brain barrier, contrast enhancement is generally due to the presence of iodinated contrast agent within the intravascular space. The radiographic enhancement of vascular lesions, such as arteriovenous malformations and aneurysms, depends on the iodine content of the circulating blood pool.

In tissues with a break in the blood-brain barrier, contrast agent accumulates within interstitial spaces of the brain. The time to maximum contrast enhancement can vary from the time that peak blood iodine levels are reached to one 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. The mechanism by which this occurs is not clear.

IN PATIENTS WITH NORMAL BLOOD-BRAIN BARRIERS and RENAL FAILURE, iodinated contrast agents have been associated with blood-brain barrier DISRUPTION and ACCUMULATION OF CONTRAST IN THE BRAIN. (See PRECAUTIONS.)

The usefulness of contrast enhancement for the investigation of the retrobulbar space and of low grade or infiltrative glioma has not been demonstrated. Calcified lesions are less likely to enhance. The enhancement of tumors after therapy may decrease. The opacification of the inferior vermis following contrast agent administration has resulted in false-positive diagnosis. Cerebral infarctions of recent onset may be better visualized with contrast enhancement. Older infarctions may be obscured by the contrast agent.

For information on coagulation parameters, platelets, erythrocytes and complement system, please refer to the LABORATORY TEST FINDINGS section.

CLINICAL TRIALS

VISIPAQUE (iodixanol) Injection was administered to 1244 adult patients. The comparators administered to 861 adult patients included low osmolar nonionic, and high and low osmolar ionic contrast media. Approximately one-half (590) of the VISIPAQUE patients were 60 years of age or older; the mean age was 56 years (range 18-90). Of the 1244 patients, 806 (65%) were male and 438 (35%) were female. The racial distribution was: Caucasian-85%, Black-12%, Oriental <1%, and other or unknown-3%. The demographic information for the pool of patients who received a comparison contrast agent was similar.

There were 1235 patients given VISIPAQUE and 855 patients given other contrast agents were evaluated for efficacy. Efficacy assessment was based on quality of the radiographic diagnostic visualization (i.e., either excellent, good, poor, or none) and on the ability to make a diagnosis (i.e., either confirmed a previous diagnosis, found normal, or diagnosed new findings). Results were compared to those of active controls (ioxaglate, iohexol, iopromide, and meglumine-sodium diatrizoate) at concentrations which were similar to those of VISIPAQUE Injection.

INTRA-ARTERIAL ADMINISTRATION

Angiocardiography, cerebral arteriography, peripheral arteriography, and visceral arteriography were studied with either one or both concentrations of VISIPAQUE Injection (270 mgI/mL or 320 mgI/mL). In these intra-arterial studies, diagnostic visualization ratings were good or excellent in 100% of the patients and a radiologic diagnosis was made in all (100%) of the patients given VISIPAQUE Injection. In additional intra-arterial studies, overall quality of diagnostic visualization was rated optimal in the majority of patients and a radiologic diagnosis was made in all (100%) of the patients administered VISIPAQUE Injection. Results were compared to those of active controls (ioxaglate, iohexol, iopromide). The number of patients studied in each indication is provided below.

Angiocardiography was evaluated in two randomized, double-blind clinical trials in 101 adult patients given VISIPAQUE Injection 320 mgI/mL and 97 given iohexol 350 mgI/mL. Seven additional angiocardiography studies were performed in 217 adult patients given VISIPAQUE Injection 320 mgI/mL, 37 given iohexol 350 mgI/mL, 40 given meglumine-sodium diatrizoate 370 mgI/mL, and 96 given ioxaglate 320 mgI/mL. Visualization ratings were good or excellent in 100% of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of the active controls. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Cerebral arteriography was evaluated in two randomized, double-blind clinical trials in 51 adult patients given VISIPAQUE Injection 320 mgI/mL and 48 given iohexol 300 mgI/mL. Two additional cerebral arteriography studies were performed in 15 adult patients given VISIPAQUE Injection 270 mgI/mL, 40 patients given VISIPAQUE Injection 320 mgI/mL, and 40 patients given ioxaglate 320 mgI/mL. Visualization ratings were good or excellent in 100% of the patients given VISIPAQUE a radiologic diagnosis was made in the majority of the patients. The results were similar to those of the active controls. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Peripheral arteriography was evaluated in two randomized, double-blind clinical trials in 49 adult patients given VISIPAQUE Injection 320 mgI/mL, 25 given iohexol 350 mgI/mL, and 25 given ioxaglate 320 mgI/mL. Four additional peripheral arteriography studies were performed in 41 adult patients given VISIPAQUE Injection 270 mgI/mL, 85 patients given VISIPAQUE Injection 320 mgI/mL, 37 given iohexol 300 mgI/mL, and 47 given iopromide 300 mgI/mL. Visualization ratings were good or excellent in 100% of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of the active controls. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Visceral arteriography was evaluated in two randomized, double-blind clinical trials in 55 adult patients given VISIPAQUE Injection 320 mgI/mL, 26 given iohexol 350 mgI/mL, and 25 given ioxaglate 320 mgI/mL. Visualization ratings were good or excellent in 100% of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. The results were similar to iohexol. Confirmation of the radiologic findings by other diagnostic methods was not obtained. The risk added to renal arteriography by giving VISIPAQUE could not be analyzed.

Similar studies with digital subtraction angiography (DSA) were completed with comparable findings noted in cerebral arteriography, peripheral arteriography, and visceral arteriography. Studies have not been conducted to determine the lowest effective concentration.

INTRAVENOUS ADMINISTRATION

Excretory urography, contrast-enhanced computed tomography (CECT) of the head, CECT of the body, and peripheral venography were studied with either one or both VISIPAQUE Injection concentrations (270 mgI/mL or 320 mgI/mL). In these intravenous studies, diagnostic visualization ratings were good or excellent in 96-100% of the patients and a radiologic diagnosis was made in all (100%) of the patients given VISIPAQUE Injection. Results were compared to those of the active control. The number of patients studied in each indication is provided below.

Excretory urography was evaluated in one uncontrolled, unblinded clinical trial in 40 patients, 20 given VISIPAQUE Injection 270 mgI/mL and 20 given VISIPAQUE Injection 320 mgI/mL, and in two randomized, double-blind clinical trials in 50 adult patients given VISIPAQUE Injection 270 mgI/mL, 50 patients given VISIPAQUE Injection 320 mgI/mL, and 50 patients given iohexol 300 mgI/mL. Visualization ratings were good or excellent in 100% of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of the active control. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

CECT of the head was evaluated in two randomized, double-blind clinical trials in 49 adult patients given VISIPAQUE Injection 270 mgI/mL, in 50 patients given VISIPAQUE Injection 320 mgI/mL, and in 49 patients given iohexol 300 mgI/mL. CECT of the body was evaluated in three randomized, double-blind clinical trials in 104 adult patients given VISIPAQUE Injection 270 mgI/mL, in 109 patients given VISIPAQUE Injection 320 mgI/mL, and in 101 patients given iohexol 300 mgI/mL. In both CECT of the head and body, visualization ratings were good or excellent in 100% of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of active controls. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Peripheral venography was evaluated in two randomized, double-blind clinical trials in 46 adult patients given VISIPAQUE Injection 270 mgI/mL and in 50 patients given iohexol 300 mgI/mL. Visualization ratings were good or excellent in 100% of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of the active control. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

INDICATIONS AND USAGE

INTRA-ARTERIAL*

VISIPAQUE Injection (270 mgI/mL) is indicated for intra-arterial digital subtraction angiography.

VISIPAQUE Injection (320 mgI/mL) is indicated for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography.

INTRAVENOUS*

VISIPAQUE Injection (270 mgI/mL) is indicated for CECT imaging of the head and body, excretory urography, and peripheral venography.

VISIPAQUE Injection (320 mgI/mL) is indicated for CECT imaging of the head and body, and excretory urography.

* For information on the concentrations and doses for the pediatric population see the PRECAUTIONS–Pediatric Use, CLINICAL PHARMACOLOGY–Special Populations, and DOSAGE AND ADMINISTRATION sections.

CONTRAINDICATIONS

VISIPAQUE Injection is not indicated for intrathecal use.

In the pediatric population prolonged fasting and the administration of a laxative before VISIPAQUE injection are contraindicated.

WARNINGS

SERIOUS 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. 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, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiocardiographic 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.

Serious or rare 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 reaction associated with the use of any contrast agent.

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

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinaceous diseases, who are prone to disease induced renal insufficiency and/or renal failure. Although neither the contrast agent nor dehydration has been proven to be the cause of renal insufficiency (or worsening renal insufficiency) in myelomatous patients, it has been speculated that the combination of both may be causative. Special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients is not recommended since it may predispose the patient to precipitation of the myeloma protein.

Reports of thyroid storm following the intravascular use of iodinated radiopaque contrast 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 agent.

Administration of radiopaque materials to patients known to have, 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 the treatment of hypertensive crisis should be readily available. These patients should be monitored very closely during contrast-enhanced procedures.

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

PRECAUTIONS

GENERAL: CONTRAST AGENTS ARE ASSOCIATED WITH RISK AND INCREASED RADIATION EXPOSURE, AND THE DECISION TO USE ENHANCEMENT SHOULD BE BASED UPON A CAREFUL EVALUATION OF CLINICAL, OTHER RADIOLOGIC DATA, AND THE RESULTS OF UNENHANCED CT FINDINGS.

Patients receiving contrast agents, and especially those who are medically unstable, must be closely supervised. 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.

Pediatrics: Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dL. Pediatric patients with immature renal function or dehydration may be at increased risk for adverse events due to prolonged elimination of iodinated contrast agents.

The injection rates in small vascular beds, and the relationship of the administered volume or concentration of iodinated contrast agents in small neonates, infants and small pediatric patients, have not been established. Caution should be exercised in selecting the volume.

Dehydration, Renal Insufficiency, Congestive Heart Failure: Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, congestive heart disease, diabetic patients, and other patients such as those on medications which alter renal function and the elderly with age-related renal impairment. Patients should be adequately hydrated prior to and following intravascular administration of iodinated contrast agent. Dose adjustments in renal impairment have not been studied.

Iodinated contrast agents may cross the blood-brain barrier. In patients where the blood-brain barrier is known or suspected to be disrupted, or in patients with normal blood-brain barrier and associated renal impairment, CAUTION MUST BE EXERCISED IN THE USE OF AN IODINATED CONTRAST AGENT. (See PHARMACODYNAMICS.)

Patients with congestive heart failure receiving concurrent diuretic therapy may have relative intravascular volume depletion, which may affect the renal response to the contrast agent osmotic load. These patients should be observed following the procedure to detect delayed hemodynamic renal function disturbances.

Immunologic Reactions: The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered. Increased risk is associated with a history of a previous reaction to contrast agent, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, drug, or food allergies), other hypersensitivities, and underlying immune disorders, autoimmunity or immunodeficiencies that predispose to specific or nonspecific mediator release. If during administration there is evidence of an allergy-like reaction, the injection should be discontinued and appropriate treatment initiated.

Skin testing cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. A thorough medical history with emphasis on allergy and hypersensitivity, immune, autoimmune and immunodeficiency disorders, and prior receipt of and response to the injection of any contrast agent may be more accurate than pretesting in predicting potential adverse reactions.

Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. Extreme caution should be exercised in considering the use of iodinated contrast agents in patients with these histories or disorders. Patients with a history of allergy or drug reaction should be observed for several hours after drug administration.

Anesthesia: General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions have been reported in these patients. It is not clear if this is due 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 a contrast agent.

Angiocardiography: In angiographic procedures, the possibility of dislodging plaques, or damaging or perforating the vessel wall with resultant pseudoaneurysms, hemorrhage at puncture site, dissection of coronary artery, etc., should be considered during catheter manipulations and contrast agent injection. Angiography may be associated with local and distal organ damage, ischemia, thrombosis and organ failure (e.g., brachial plexus palsy, chest pain, myocardial infarction, sinus arrest, hepatorenal function abnormalities, etc.). Test injections to ensure proper catheter placement are suggested. During these procedures, increased thrombosis and activation of the complement system has also occurred. (See WARNINGS.)

Angiocardiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism. (See PHARMACODYNAMICS.)

In an uncontrolled study of 204 patients who received VISIPAQUE Injection and who had cardiovascular disease associated with either Class II-IV congestive failure, angina, recent myocardial infarction, left ventricular ejection fraction of <35% or valvular disease, the patients were evaluated for the types of interventions needed for treatment of adverse events. The reported type and frequency of adverse events were comparable to those in all clinical intra-arteriographic studies. Of 204 patients, 63 (31%) of patients had 99 adverse events. Of the 99 events, 68 (68%) required medical intervention of some type. Patients with 17 (17%) of these adverse events required treatment with cardioversion, multiple medications, prolonged hospitalization or intensive care. These interventions were not compared to a control group of similar patients who did not have coronary arteriography.

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

Venography: In addition to the general precautions previously described, special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection, venous thrombosis or a totally obstructed venous system.

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

GENERAL ADVERSE REACTIONS WITH CONTRAST AGENTS

The following adverse reactions are possible with any parenterally administered iodinated contrast agent. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or five to ten 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 other iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%).

The reported incidence of adverse reactions to contrast agents in patients with a history of allergy is twice that of the general population. Patients with a history of a previous reaction to a contrast agent 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 agents fall into two categories: chemotoxic reactions and idiosyncratic reactions. Chemotoxic reactions result from the physicochemical properties of the contrast agent, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast agent 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.

INFORMATION FOR PATIENTS

Patients receiving an iodinated intravascular contrast agent should be instructed to:

1. Inform your physician if you are pregnant (see PRECAUTIONS - Pregnancy Category B).
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 have immune, autoimmune or immune deficiency disorders. Also inform your physician if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS, General).
4. Inform your physician about all medications you are currently taking, including nonprescription (over-the-counter) drugs, before you have this procedure.

DRUG INTERACTIONS

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

Other drugs should not be mixed with VISIPAQUE Injection.

DRUG/LABORATORY TEST INTERACTIONS

The results of protein bound iodine and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for at least 16 days following administration of iodinated contrast agents. However, thyroid function tests which do not depend on iodine estimations (e.g., T_3 resin uptake and total or free thyroxine T_4 assays) are not affected.

As reported with other contrast agents, VISIPAQUE may produce a false-positive result for protein in the urine using Multistix®. However, the Coomassie blue method has been shown to give accurate results for the measurement of urine protein in the presence of VISIPAQUE. In addition, care should be used in interpreting the results of urine specific gravity measurements in the presence of high levels of VISIPAQUE and other contrast agents in the urine. Refractometry or urine osmolality may be substituted.

LABORATORY TEST FINDINGS

Coagulation, platelets, erythrocytes and complement activation were evaluated with standard citrated human plasma or whole blood in the following assays: thrombin generation time, platelet aggregation and activation, red blood cell rigidification and aggregation, and complement activation. Data on reversibility, thrombin time, PTT and clotting factors are not available.

In vitro human blood studies showed that with 5 mL of iodixanol 320 mgI/mL, the thrombin generation time was increased to a mean of 46 minutes (saline control = 14 minutes). An *in vitro* study of platelet enriched plasma after incubation with iodixanol 320 mgI/mL, the platelet aggregation response to collagen was inhibited to 63% of normal (range 30-98% with iodixanol concentrations of 16 to 64 mgI/mL); these findings were comparable to those of a tested nonionic comparators; platelet degranulation did not occur. Erythrocyte rigidification (measured by half conductance of the Mynipore sieve with hematocrit adjusted to 8%) was comparable for iodixanol and the tested nonionic comparators. Also, the red cell aggregation decrease was comparable to that of other nonionic comparators. In a CH-50 hemolytic complement activation assay after 11 hours of incubation with 320 mgI/mL, the remaining complement activity was approximately 15 % ($\pm$ 3) of normal.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed with iodixanol to evaluate carcinogenic potential. Iodixanol was not genotoxic in a series of studies including the Ames test, the CHO/HGPRT assay, a chromosome aberration assay in CHO cells, and a mouse micronucleus assay. Iodixanol did not impair the fertility of male or female rats when administered at doses up to 2.0 gI/kg (1.3 times the maximum recommended dose for a 50 kg human, or approximately 0.2 times the maximum recommended dose for a 50 kg human following normalization of the data to body surface area estimates).

PREGNANCY

Teratogenic Effects: Pregnancy Category B

Reproduction studies performed in rats and rabbits at doses up to 2.0 gI/kg (1.3 times the maximum recommended dose for a 50 kg human, or approximately 0.2 (rat) and 0.4 (rabbit) times the maximum recommended dose for a 50 kg human following normalization of the data to body surface estimates) have not revealed evidence of impaired fertility or harm to the fetus due to iodixanol. Adequate and well-controlled studies in pregnant women have not been conducted. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

NURSING MOTHERS

It is not known whether VISIPAQUE Injection 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 agents are administered to nursing women because of the potential for adverse reactions, and consideration should be given to temporarily discontinue nursing.

PEDIATRIC USE

The safety and efficacy of VISIPAQUE has been established in the pediatric population over 1 year of age for arterial studies and for intravenous procedures. Use of VISIPAQUE in these age groups is supported by evidence from adequate and well controlled studies of VISIPAQUE in adults and additional safety data obtained in pediatric studies. Although VISIPAQUE has been administered to pediatric patients less than 1 year of age, the relative safety of the volumes injected, the optimal concentrations, and the potential need for dose adjustment because of prolonged elimination half-lives have not been systematically studied. (See CLINICAL PHARMACOLOGY–Special Populations section).

VISIPAQUE (iodixanol) Injection was administered to 459 pediatric patients. There were 26 patients administered VISIPAQUE Injection in the birth to <29 day age range, 148 from 29 days to 2 years, 263 from 2 to <12 years, and 22 from 12 to 18 years. The mean age was 4.4 years (range <1 day to 17.4 years). Of the 459 patients, 252 (55%) were male and 207 (45%) were female. The racial distribution was: Caucasian-81%, Black-14%, Oriental-2%, and other or unknown-4%. The demographic information for the pool of patients who received a comparison contrast agent was similar.

In pediatric patients who received intravenous injection for computerized tomography or excretory urography, a concentration of 270 mgI/mL was used in 144 patients, and a concentration of 320 mgI/mL in 154 patients. All patients received one intravenous injection of 1-2 mL/kg.

In pediatric patients who received intra-arterial and intracardiac studies, a concentration of 320 mgI/mL was used in 161 patients. Of the 161 patients in the intra-arterial studies, the mean age was 2.6 years. Twenty-two patients were < 29 days of age; 78 were 29 days to 2 years of age; and 61 were over 2 years. Most of these pediatric patients received initial volumes of 1-2 mL/kg and most patients had a maximum of 3 injections.

Optimal volumes, concentrations or injection rates of VISIPAQUE have not been established because different injection volumes, concentrations, and injection rates were not studied. The relationship of the volume of injection with respect to the size of the target vascular bed has not been established. The potential need for dose adjustment to maximize efficacy of computerized tomography, or to minimize the toxicity to other immature body tissues, has not been studied in neonates or infants with immature renal function.

In the above patients, adverse events were associated with decreasing age and intra-arterial procedures. In general the type of adverse events reported are similar to those of adults. Although the frequency of events appears to be comparable, the percent-ages cannot be confirmed because of the different ability of pediatric and adult patients to report adverse events.

ADVERSE EVENTS REPORTED IN PEDIATRIC PATIENTS WHO RECEIVED VISIPAQUE (BY AGE, ROUTE OF ADMINISTRATION, AND CONCENTRATION OF IODINE)

Age Range	Number of Patients with Adverse Events	
< 29 days	8/24 (33%)	*P* < 0.05 between the < 29 days and 1-2 year patient groups.
> 29 days - 6 months	9/43 (20%)	
> 6 months - 12 months	26/91 (28%)	
1 year - 2 year	8/49 (17%)	
> 2 years	40/263 (15%)	
Intra-arterial injections	42/161 (26%)	*P* < 0.05
Intravenous injections	32/298 (10%)	
270 mgI/mL	11/144 (8%)	*P* < 0.05
320 mgI/mL	53/315 (17%)	

(For additional information see the CLINICAL PHARMACOLOGY–Special Populations, and DOSAGE AND ADMINISTRATION sections.)

GERIATRIC USE

Of the total number of patients in clinical studies of VISIPAQUE in the U.S., 254/757 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of

decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE EVENTS

VISIPAQUE (iodixanol) Injection was administered to 1244 patients. The comparators administered to 861 patients included low osmolar nonionic, and high and low osmolar ionic contrast media. For complete demographics, see CLINICAL TRIALS section.

Serious, life-threatening and fatal reactions have been associated with the administration of iodine-containing contrast media, including VISIPAQUE Injection. In clinical trials, 3/1244 patients given VISIPAQUE Injection and 1/861 patients given a comparator died within 5 days or later after drug administration. Also, 7/1244 patients given VISIPAQUE Injection and 8/861 given a comparator had serious adverse events. Rare reports of anaphylaxis have been documented during postmarket surveillance.

As with other contrast agents, VISIPAQUE is often associated with sensations of discomfort, warmth or pain. In a subgroup of 1259 patients, for whom data are available; similar percentages of patients (30%) who received VISIPAQUE or a comparator had application site discomfort, pain, warmth or cold. VISIPAQUE had a trend toward fewer patient reports of moderate or severe pain or warmth; however, whether or not this related to the dose, rate of administration, site of injection or concentration has not been determined.

The following table of incidence of events is based upon blinded, controlled clinical trials with VISIPAQUE Injection in controlled clinical studies in which VISIPAQUE (1244 patients) was compared with low osmolar nonionic (iohexol, iopromide), a low osmolar ionic (ioxaglate), and a high osmolar ionic (diatrizoate) contrast agents. This listing includes all reported adverse events regardless of attribution. Adverse events (AEs) are listed by body system and in decreasing order of occurrence greater than 0.5% in the VISIPAQUE group.

As the table shows, one or more adverse events were recorded in 248 of 1244 (20%) patients during the clinical trials, with the administration of VISIPAQUE Injection or within the defined duration of the study follow-up period (24 to 72 hours). In intravenous and intra-arterial procedures, the incidence and type adverse reaction was similar to those of the studied nonionic comparators (iohexol). In a 757 patient subgroup for which data are available, women reported more adverse events 83/299 (27.8%) than men 77/458 (16.2%). Women reported more chest pain (9/299 or 3%) than men (4/458 or 0.8%).

EACH ADVERSE EVENT REPORTED IN CONTROLLED CLINICAL TRIALS IN GREATER THAN 0.5% OF THE ADULT VISIPAQUE INJECTION PATIENTS

NUMBER OF PATIENTS EXPOSED		VISIPAQUE N=1244	Pooled Comparators N=861
Number of Patients With Any Adverse Event		248 (19.9%)	194 (22.5%)
Body As a Whole	Patients With Any Event	41 (3.3%)	22 (2.6%)
	Edema (any location)	7 (0.6%)	0 (0%)
Cardiovascular	Patients With Any Event	37 (3.0%)	39 (4.5%)
	Angina Pectoris/Chest Pain	28 (2.2%)	22 (2.6%)
Gastrointestinal	Patients WIth Any Event	51 (4.1%)	46 (5.3%)
	Diarrhea	7 (0.6%)	6 (0.7%)
	Nausea	35 (2.8%)	32 (3.7%)
	Vomiting	10 (0.8%)	11 (1.3%)
Nervous System	Patients With Any Event	101 (8.1%)	60 (7.0%)
	Agitation, Anxiety, Insomnia, Nervousness	10 (0.8%)	0 (0%)
	Dizziness	8 (0.7%)	8 (0.9%)
	Headache/Migraine	31 (2.5%)	15 (1.7%)
	Paresthesia	12 (1.0%)	1 (0.1%)
	Sensory Disturbance	10 (0.8%)	9 (1.0%)
	Syncope	8 (0.6%)	1 (0.1%)
	Vertigo	30 (2.4%)	20 (2.3%)
Skin	Patients With Any Event (a)	42 (4.6%)	18 (2.1%)
	Nonurticarial Rash or Erythema	26 (2.1%)	4 (0.5%)
	Pruritus	20 (1.6%)	3 (0.3%)
	Urticaria	6 (0.5%)	10 (1.2%)
Special Senses	Patients With Any Event	57 (4.6%)	38 (4.4%)
	Parosmia	6 (0.5%)	4 (0.5%)
	Taste Perversion	43 (3.5%)	32 (3.7%)
	Scotoma	14 (1.1%)	2 (0.2%)

(a) Does not include application site.

The following selected adverse events were reported in ≤0.5% of the 1244 patients in controlled clinical trials who received VISIPAQUE Injection.

Body as a Whole—General Disorders: back pain, fatigue, malaise.

Cardiovascular Disorders: arrhythmias, cardiac failure, conduction abnormalities, hypotension, myocardial infarction.

Nervous System: cerebral vascular disorder, convulsions, hypoesthesia, stupor, confusion.

Gastrointestinal System Disorders: dyspepsia.

Hypersensitivity Disorders: pharyngeal edema.

Respiratory System Disorders: asthma, bronchitis, dyspnea, pulmonary edema, rhinitis.

Renal System Disorders: abnormal renal function, acute renal failure, hematuria.

Peripheral Vascular Disorders: flushing, peripheral ischemia.

Skin and Appendage Disorders: hematoma, increased sweating.

Special Senses, Other Disorders: tinnitus.

Vision Disorders: abnormal vision.

Additional adverse events reported in other clinical studies and in foreign postmarketing surveillance and foreign clinical trials with the use of VISIPAQUE Injection are: anaphylactic reactions, anaphylactoid reactions, hypoglycemia, amnesia, cardiac arrest, hypertension, dyskinesia, hemorrhage not otherwise specified, polymyalgia rheumatica, pulmonary embolism, respiratory depression, and cortical blindness.

PEDIATRICS

For demographics, see PEDIATRIC USE section.

The overall character, quality, and severity of adverse reactions in pediatric patients is similar to that reported in adult populations from domestic and foreign postmarketing surveillance and other information. Selected commonly reported adverse events in pediatrics include: vomiting, nausea, fever, rash, and pruritus. Less frequently reported events are apnea, disseminated intravascular coagulation, atrioventricular block and bundle branch block, arrhythmia, cardiac failure, renal failure and taste perversion.

OVERDOSAGE

The adverse effects of overdosage of any contrast agent may be life-threatening and affect mainly the pulmonary and cardiovascular systems. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy. VISIPAQUE Injection does not bind to plasma or serum protein and can be dialyzed.

DOSAGE AND ADMINISTRATION

For Pediatric dosing see the end of this Dosage and Administration section.

GENERAL

The combination of volume and concentration of VISIPAQUE Injection to be used should be individualized, accounting for factors such as age, body weight, size of the vessel, and rate of blood flow within the vessel. Specific dose adjustment studies for age, gender, weight and renal function have not been conducted with VISIPAQUE. As with other iodinated contrast agents, lower doses may have less risk. The efficacy of VISIPAQUE Injection below doses recommended has not been established. Other factors, such as pathology anticipated, 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.

The maximum recommended total dose of iodine is 80 grams.

If an adverse reaction occurs during injection, consider stopping the injection immediately if warranted by the nature and severity of the event.

Patients should be adequately hydrated prior to and following the intravascular administration of iodinated contrast agents (see WARNINGS and PRECAUTIONS).

INTRA-ARTERIAL ADMINISTRATION

VISIPAQUE 320 mgI/mL is recommended for intra-arterial injection in the radiographic contrast evaluation of arterial lesions of the brain, the coronary arteries and left ventricle, and for intra-arterial injection in the radiographic contrast evaluation of peripheral arteries. VISIPAQUE is also recommended for intra-arterial digital subtraction angiography, as specified in the dosing chart below.

Injection rates should be approximately equal to the flow rate in the vessel being injected. The volume required will depend on the size, flow rate, and disease state of the injected vessel, on the size and condition of the patient, and on the imaging technique used. The usual single injection volumes or total dose per patient (mL/kg) for adults and adolescents over 12 years of age are listed in the tables below.

ADULTS and ADOLESCENTS OVER 12 YEARS OF AGE USUAL SINGLE DOSES FOR INJECTION INTO SELECTED ARTERIES				
	ARTERIOGRAPHY	IA-DSA*		
Intra-Arterial Injection Sites	320 mgI/mL	270 mgI/mL	320 mgI/mL	Maximum Total Dose
Carotid Arteries	10 - 14 mL		5 - 8 mL	Usually Not to
Vertebral Arteries	10 - 12 mL		5 - 8 mL	Exceed 175 mL
Right Coronary Artery	3 - 8 mL			Usually Not to
Left Coronary Artery	3 - 10 mL			Exceed 200 mL
Left Ventricle	20 - 45 mL			
Renal Arteries	8 - 18 mL	10 - 25 mL	—	Usually Not to
Aortography	30 - 70 mL	20 - 50 mL	10 - 50 mL	Exceed 250 mL
Major Branches of Aorta	10 - 70 mL	5 - 30 mL	2 - 10 mL	
Aortofemoral Runoffs	20 - 90 mL	—	6 - 15 mL	
Peripheral Arteries	15 - 30 mL	—	3 - 15 mL	

*IA-DSA = Intra-Arterial Digital Subtraction Angiography

INTRAVENOUS ADMINISTRATION

Contrast Enhanced Computed Tomography (CECT)

Intravenous administration of VISIPAQUE Injection (270 mgI/mL and 320 mgI/mL) is recommended for contrast enhancement in the evaluation of neoplastic and nonneoplastic lesions of the head and body (intrathoracic, intra-abdominal and retroperitoneal regions), evaluations of renal function, and evaluations of the peripheral venous system. Selected dosing for different indications in adults and pediatric patients are shown in the following tables.

ADULTS and ADOLESCENTS OVER 12 YEARS OF AGE USUAL VISIPAQUE DOSING FOR INTRAVENOUS CONTRAST ADMINISTRATION				
Study Type	Comment	270 mgI/mL	320 mgI/mL	Maximum Total Volume
CECT of Head or Body	Bolus Infusion	75 - 150 mL 100 - 150 mL	75 - 150 mL 100 - 150 mL	150 mL
Excretory Urography	Normal Renal Function	1 mL/kg	1 mL/kg	100 mL
Venography	Per lower extremity	50 - 150 mL		250 mL

PEDIATRIC DOSING

The recommended dose in children over 1 year of age for the evaluation of:

Intra-arterial Administration for Cerebral, Cardiac chambers and related major arteries, and Visceral Studies:

VISIPAQUE 320 mgI/mL as 1 to 2 mL/kg. The recommended total dose of VISIPAQUE should not exceed 4 mL/kg.

Intravenous Administration for Contrast Enhanced Computerized Tomography or Excretory Urography:

VISIPAQUE 270 mgI/mL as 1 to 2 mL/kg. The recommended total dose of VISIPAQUE should not exceed 2 mL/kg.

The safety and efficacy relationships of other doses, concentrations or procedures have not been established. (See CLINICAL PHARMACOLOGY–Special Populations, and PRECAUTIONS–Pediatric Use sections.)

The maximum total dose of iodine in the pediatric population has not been established.

DRUG HANDLING

As with all contrast agents because of the potential for chemical incompatibility, VISIPAQUE Injection should not be mixed with, or injected in, intravenous administration lines containing other drugs, solutions or total nutritional admixtures.

Sterile technique must be used in all procedures involving vascular injections of contrast agents.

VISIPAQUE Injection may be administered at body temperature as well as at room temperature.

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 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.

HOW SUPPLIED

VISIPAQUE (iodixanol) Injection 270 mgI/mL:

50 mL vial, boxes of 10 (NDC 0407-2222-01)
50 mL glass bottle, boxes of 10 (NDC 0407-2222-06)
50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-16)
100 mL glass bottle, boxes of 10 (NDC 0407-2222-02)
100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-17)
150 mL glass bottle, boxes of 10 (NDC 0407-2222-03)
150 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-19)
200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-21)

VISIPAQUE (iodixanol) Injection 320 mgI/mL:

50 mL vial, boxes of 10 (NDC 0407-2223-01)
50 mL glass bottle, boxes of 10 (NDC 0407-2223-06)
50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-16)
100 mL glass bottle, boxes of 10 (NDC 0407-2223-02)
100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-17)
150 mL glass bottle, boxes of 10 (NDC 0407-2223-03)
150 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-19)
200 mL glass bottle, boxes of 10 (NDC 0407-2223-04)
200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-21)

FEDERAL GOVERNMENT CODES

VISIPAQUE (iodixanol) Injection 270 mgI/mL:

50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-52)
100 mL glass bottle, boxes of 10 (NDC 0407-2222-50)
100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-53)
150 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-54)
200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2222-55)

VISIPAQUE (iodixanol) Injection 320 mgI/mL:

50 mL glass bottle, boxes of 10 (NDC 0407-2223-50)
50 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-54)
100 mL glass bottle, boxes of 10 (NDC 0407-2223-51)
100 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-55)
150 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-56)
200 mL glass bottle, boxes of 10 (NDC 0407-2223-53)
200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-57)

Protect VISIPAQUE Injection from strong daylight and direct exposure to sunlight. VISIPAQUE should be stored at controlled room temperature, 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

VISIPAQUE Injection in all presentations may be stored in a contrast media warmer for up to one month at 37°C (98.6°F).

Do not freeze or use if the product is inadvertently frozen. Freezing may compromise the closure integrity of these packages.

SPECIAL HANDLING AND STORAGE FOR POLYMER BOTTLES ONLY.
DO NOT USE IF TAMPER-EVIDENT RING IS BROKEN OR MISSING.

GE Healthcare

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