

ULTRAVIST® (brand of iopromide) INJECTION

150	240
300	370

NOT FOR INTRATHECAL USE

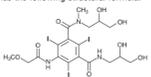
ULTRAVIST® Injection 150 mg/mL
ULTRAVIST® Injection 240 mg/mL
ULTRAVIST® Injection 300 mg/mL
ULTRAVIST® Injection 370 mg/mL
Nonionic contrast agents

Rx only

DESCRIPTION

ULTRAVIST® (iopromide) Injection is a nonionic, water soluble x-ray contrast agent for intravascular administration. The chemical name for iopromide is *N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-N-methyl-1,3,5-benzeneisocarboxamide*. Iopromide has a molecular weight of 791.12 (iodine content 48.12%).

Iopromide has the following structural formula:



ULTRAVIST® Injection is a nonionic, sterile, clear, colorless to slightly yellow, odorless, pyrogen-free aqueous solution of iopromide, which is available in four strengths: ULTRAVIST® Injection 150 mg/mL, ULTRAVIST® Injection 240 mg/mL, ULTRAVIST® Injection 300 mg/mL, and ULTRAVIST® Injection 370 mg/mL.

Each mL of ULTRAVIST® Injection 150 mg/mL provides 311.70 mg iopromide, with 2.42 mg tromethamine as a buffer and 0.1 mg edetate calcium disodium as a stabilizer. Each mL of ULTRAVIST® Injection 240 mg/mL provides 498.72 mg iopromide, with 2.42 mg tromethamine as a buffer and 0.1 mg edetate calcium disodium as a stabilizer.

Each mL of ULTRAVIST® Injection 300 mg/mL provides 768.86 mg iopromide, with 2.42 mg tromethamine as a buffer and 0.1 mg edetate calcium disodium as a stabilizer.

During the manufacture of ULTRAVIST® Injection, sodium hydroxide or hydrochloric acid may be added for pH adjustment. ULTRAVIST® Injection has a pH of 7.4 (6.5 – 8.0) at 25±2°C, is sterilized by autoclaving and contains no preservatives.

The iodine concentrations (mg/mL) available have the following physicochemical properties:

Property	150 mg/mL	240 mg/mL	300 mg/mL	370 mg/mL
Osmolality (mOsm/kg)				
@ 37°C	328	483	607	774
Osmolality (mOsm/L)				
@ 37°C	278	368	428	496
Viscosity (cP) @ 20°C	2.3	4.9	9.2	22.0
@ 37°C	1.5	2.8	4.9	10.0
Density (g/mL)				
@ 20°C	1.164	1.262	1.330	1.409
@ 37°C	1.157	1.252	1.322	1.399

*Osmolality was measured by vapor-pressure osmometry. Osmolality was calculated from the measured osmotic concentrations.

Solutions of ULTRAVIST® Injection 150 mg/mL, 240 mg/mL, 300 mg/mL, and 370 mg/mL have osmolalities from approximately 1.1 to 2.7 times that of plasma (285 mOsm/kg water).

CLINICAL PHARMACOLOGY

General Iopromide is a nonionic, water soluble, tri-iodinated x-ray contrast agent for intravascular administration. Intravascular injection of iopromide opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant hemolysis occurs.

In healthy young male volunteers receiving ULTRAVIST® Injection intravenously in doses corresponding to 15.0 or 80.0 g iodine, the pharmacokinetic data were as follows: Mean total clearance was 1.1 to 2.7 times that of plasma (285 mL/min/kg). The compound is predominantly distributed in the extracellular space as suggested by a steady-state volume of distribution of 16. Iopromide's plasma protein binding is 1% and negligible. The mean terminal half-life was approximately 107 minutes and 104 mL·min⁻¹, respectively. After an initial fast distribution phase with a half-life of 0.24 hour, a slow elimination phase with a half-life of 2.0 hours and a main elimination phase with a half-life of 6.2 hours were observed. However, during the terminal phase only 3% of the dose is eliminated; 97% of the dose is disposed of during the earlier phases, the largest part of which occurs during the main elimination phase. The distribution half-life of iopromide to the creatinine clearance is 0.82 suggesting that iopromide is mainly excreted by glomerular filtration. Additional tubular reabsorption is possible.

In middle-aged and elderly patients without significantly impaired renal function, the mean total clearance of iopromide corresponding to 9.0–30.0 g iodine, the mean steady-state volume of distribution ranged between 30–40 L, indicating partitioning of the drug into the intracellular space in addition to extracellular distribution. Mean total renal clearances are between 81–125 mL·min⁻¹ and 70–115 mL·min⁻¹, respectively in these patients, and are similar to the values found in the young volunteers. The distribution half-life in this patient population is 0.1 hour, the main elimination phase half-life is 2.3 hours, and the terminal elimination phase half-life is 40 hours. Iopromide binds negligibly to plasma or serum proteins.

The amounts excreted unchanged in urine represent 97% of the dose in young healthy subjects. Only 2% of the dose is recovered in the feces. Similar recoveries in urine and feces are observed in middle-aged and elderly patients. This finding suggests that, compared to the renal route, biliary and/or gastrointestinal excretion is not important for ULTRAVIST® Injection.

In patients with significantly impaired renal function, total clearance of iopromide is reduced and the half-life of the terminal phase is prolonged. Also as above, the disposition of the drug in patients with renal insufficiency showed three separable phases. Total clearance depends linearly on the creatinine clearance. Dose adjustments in patients with renal impairment have not been studied. (See **Pharmacodynamics** section for renal failure and blood-brain interaction.) ULTRAVIST® Injection has been reported to be dialyzable.

In the pediatric population, the pharmacokinetics parameters have not been established. Dose optimization has not been systematically established. (See **PRECAUTIONS – PEDIATRIC USE**.)

Metabolism There is no evidence for metabolism of ULTRAVIST® Injection.

Pharmacodynamics As with other iodinated contrast agents, following ULTRAVIST® Injection, the degree of contrast enhancement is directly related to the iodine content in the administered dose; peak iodine plasma levels occur immediately following rapid intravenous 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 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).

ULTRAVIST® Injection 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 ULTRAVIST® 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 any relative differences in extravascular diffusion between adjacent tissues.

In the normal brain with an intact blood-brain barrier, contrast 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 brain tissue. The time to maximum contrast enhancement can vary from the time that peak blood iodine levels are reached to 1 hour after intravenous bolus administration. This delay suggests that radiopaque 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 vena cava following contrast agent administration has resulted in false-positive diagnosis. Cerebral infarctions of recent onset may be better visualized with contrast enhancement. Older infarctions are obscured by the contrast agent.

For information on coagulation parameters, fibrinolysis and complement system, please refer to the Laboratory Test Findings section.

CLINICAL TRIALS

ULTRAVIST® Injection was administered to 708 patients. The active control comparators, low osmolal, nonionic iodinated contrast media, were administered to 659 patients. Of 18 patients given ULTRAVIST® Injection, 1 patient was less than 18 years of age, 347 patients were between 18 and 59 years of age, and 350 patients were equal to or greater than 60 years of age; the mean age was 56.5 years (range 17–88). Of the 708 patients, 446 (63%) were male and 262 (37%) were female. The racial distribution was: Caucasian 463 (66.4%), Black 95 (13.4%), Hispanic 36 (5.1%), Asian 11 (1.6%), and other 113 (14.5%). The demographic information for the pool of patients who received a comparison iodinated contrast agent was similar.

Six hundred seventy-seven (677) patients given ULTRAVIST® Injection and 631 patients given another iodinated contrast agent were evaluated for efficacy. Efficacy assessment was based on the global evaluation of the quality of the radiographs by rating visualization as either excellent, good, poor, or no image, on the ability to make a diagnosis. Results were compared to those of active controls (ioversol, iohexol or iopamidol) at concentrations which were similar to those of ULTRAVIST® Injection.

Five (5) intra-arterial and three (3) intravenous procedures were compared in 17 of 4 concentrations (270 mg/mL, 300 mg/mL, 240 mg/mL, and 150 mg/mL). These procedures were aortography/visceral angiography, coronary arteriography and left ventriculography, cerebral arteriography, peripheral arteriography, intra-arterial digital subtraction angiography (IA-DSA), contrast-enhanced computed tomography (CECT) of head and body, excretory urography, and peripheral venography.

Cerebral arteriography was evaluated in 2 randomized, double-blind clinical trials of ULTRAVIST® Injection 300 mg/mL in patients with conditions such as altered cerebrovascular perfusion and/or permeability occurring in central nervous system diseases due to various CNS disorders. Results were assessed in 80 patients with ULTRAVIST® Injection, 39 with iohexol 300 mg/mL and 43 with iopamidol 300 mg/mL. Visualization ratings were good or excellent in 99% of the patients with ULTRAVIST® Injection; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of iohexol and iopamidol. Confirmation of the radiologic findings by other diagnostic methods was not obtained. Coronary arteriography/left ventriculography was evaluated in 2 randomized, double-blind clinical trials and 1 unblinded, unrandomized clinical trial of ULTRAVIST® Injection 370 mg/mL in patients with conditions such as altered coronary artery perfusion due to metabolic causes and in patients with conditions such as altered ventricular function. Results were assessed in 106 patients with ULTRAVIST® Injection, 59 with iohexol 350 mg/mL, and 21 with iopamidol 370 mg/mL. Visualization ratings were good or excellent in 99% or more of the patients with ULTRAVIST® Injection, depending on the structure evaluated; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of iohexol and iopamidol. A confirmation of the radiologic findings by other diagnostic methods was not obtained.

Aortography/visceral angiography was evaluated in 2 randomized, double-blind clinical trials in patients with conditions such as altered aortic blood flow and/or visceral vascular disorders. The results were assessed in 78 patients with ULTRAVIST® Injection 370 mg/mL, 44 with iohexol 350 mg/mL, and 33 with iopamidol 370 mg/mL. Visualization ratings were good or excellent in the majority of the patients; a radiologic diagnosis was made in 99% of the patients with ULTRAVIST® Injection. The results were similar to those of iohexol and iopamidol. A confirmation of the radiologic findings by other diagnostic methods was not obtained.

CECT of head and body was evaluated in 3 randomized, double-blind clinical trials in patients with vascular disorders. A total of 85 patients received ULTRAVIST® Injection 300 mg/mL, 40 received iohexol 300 mg/mL, and 55 received iopamidol 300 mg/mL. Visualization ratings were good or excellent in 99% of the patients with ULTRAVIST® Injection; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of iohexol and iopamidol. A confirmation of CECT findings by other diagnostic methods was not obtained.

Peripheral venography was evaluated in 2 randomized, double-blind clinical trials of ULTRAVIST® Injection 240 mg/mL in patients with disorders affecting venous drainage of the limbs. Results were assessed in 63 ULTRAVIST® Injection patients, 41 patients with iohexol 240 mg/mL and 21 with ioversol 240 mg/mL. Visualization ratings were good or excellent in 100% of the patients; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of iohexol and ioversol. A confirmation of radiologic findings by other diagnostic methods was not obtained.

INDICATIONS AND USAGE **INTRA-ARTERIAL:** ULTRAVIST® Injection (150 mg/mL) is indicated for intra-arterial digital subtraction angiography (IA-DSA). ULTRAVIST® Injection (300 mg/mL) is indicated for cerebral arteriography and peripheral arteriography. ULTRAVIST® Injection (370 mg/mL) is indicated for coronary arteriography and left ventriculography, visceral angiography, and aortography.

INTRAVENOUS: ULTRAVIST® Injection (240 mg/mL) is indicated for peripheral venography. ULTRAVIST® Injection (300 mg/mL) is indicated for contrast enhanced computed tomographic (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** and the **DOSE AND ADMINISTRATION** sections.

CONTRAINDICATIONS ULTRAVIST® Injection is not indicated for intrathecal use.

In the pediatric population prolonged fasting and the administration of a laxative before ULTRAVIST® Injection are contraindications.

SEVERE ADVERSE EVENTS – INADVERTENT INTRATHECAL ADMINISTRATION: Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis,

acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not administered intrathecally.

Nonionic iodinated contrast agents inhibit blood coagulation, *in vitro* less than ionic contrast agents. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast agents. The use of plastic syringes in place of glass may decrease but not eliminate the likelihood of *in vitro* clotting.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast agents. 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 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 agent reaction. (See **DRUG INTERACTIONS**.) 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 and DRUG INTERACTIONS**.)

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemic disease who are prone to disease-induced renal insufficiency and/or failure. Although neither the contrast agent nor dehydration has been proved 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 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. These patients should be monitored very closely during contrast enhancement procedures. Contrast agents 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 have been reported. Caution should be exercised 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 or suspected of having pheochromocytoma should be performed with extreme caution. It, 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. These patients should be monitored very closely during contrast enhancement procedures. Contrast agents may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

PRECAUTIONS

General: THE DECISION TO USE CONTRAST ENHANCEMENT IS ASSOCIATED WITH RISK. INCREASED RISK OF ALLERGY EXPOSURE, AND 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, should be kept in a fully equipped emergency cart. 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, a physician and a competent personnel should be available for at least 30 to 60 minutes after administration.

Pediatrics: Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, a sensitivity to medication and/or allergies, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dL.

The injection rates in small vascular beds, and the relationship of the dose by volume or concentration in small pediatric patients have not been established. Caution should be exercised in selecting the dose.

Dehydration, Renal Insufficiency, Congestive Heart Failure: Patients with renal insufficiency without significant hypovolemia, 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 related renal impairment. Patients should be adequately hydrated prior to and following the intravascular administration of iodinated contrast agents. Dose adjustments in renal impairment have not been studied. (See **DRUG INTERACTIONS**.)

The injection rates in small vascular beds, and the relationship of the dose by volume or concentration in small pediatric patients have not been established. Caution should be exercised in selecting the dose.

Immunologic Reactions: The possibility of a reaction, including serious, life-threatening, and fatal allergic reactions, should always be considered. Increased risk is associated with a history of previous reaction to a contrast agent, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) and other hypersensitivities, and underlying immune disorders, auto-immunity or immunodeficiencies that predispose to specific or non-specific mediator response. (See **DRUG INTERACTIONS**.) 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 use of contrast agents should be obtained. CAUTION MUST BE EXERCISED IN CONSIDERING 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. Such patients should be observed for several hours following the procedure to detect delayed hemodynamic renal function disturbances.

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.

Anesthetic: 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. It is not clear if this is due to the inability of the patient to identify warning symptoms, or to the hypotensive effect of anesthesia, which may prolong the circulation time and increase the duration of exposure to the contrast agent.

Aniography: 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, hepato-renal function abnormalities, etc.). Test injections to insure proper catheter placement are suggested. Increased thrombosis and activation of the complement system has also occurred. (See **WARNINGS**.)

Angiography also should be avoided whenever possible in patients with myelomatous disease because of the risk of inducing thrombosis and embolism. (See **Pharmacodynamics**.)

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risks. Also, the inherent risks of angiography 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 occluded 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 TO 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 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 other iodinated contrast agents range from 6.6 per 1 million (0.0066 percent) to 1 in 10,000 patients (0.01 percent).

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 previous reactions to a contrast agent are three times more susceptible than other patients. However, sensitivity to contrast agents does not appear to increase with repeated administrations.

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 nature 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 require urgent and mandatory.

Information for Patients:

Patients receiving iodinated intravascular contrast agents should be instructed to:

1. Inform your physician if you are pregnant. (See **PRECAUTIONS, PREGNANCY – Teratogenic Effects: 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 had allergic reactions to other contrast agents, or if you have any other allergic reactions. Inform your physician if you have 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 non-prescription (over-the-counter) drugs, before you have this procedure.

DRUG INTERACTIONS

In patients taking biguanides, acute alterations in renal function after iodinated contrast agents may precipitate lactic acidosis. Biguanides should be stopped 48 hours before to the contrast medium examination and should be restarted 48 hours after the procedure. (See biguanide package insert.)

Patients on beta-blockers may be unresponsive to the usual doses of epinephrine used to treat allergic reactions. Because of the risk of hypotension, epinephrine and other vasoconstrictor agents should be used with caution in patients taking beta-blockers. (See **PRECAUTIONS**.)

Interleukins are associated with an increased prevalence of delayed hypersensitivity reactions after receiving iodinated contrast agents. These reactions include fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, and oliguria. The symptoms have been reported within a few hours, as long as several months after the last dose of interleukin-2. Renal toxicity has been reported in patients with renal dysfunction who were given an oral cholestyramine agent followed by intravascular contrast agent. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholestyramine contrast agent.

Other drugs should not be mixed with ULTRAVIST® 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 estimates, e.g., T₃ resin uptake and total or free thyroxine (T₄) assays are not affected.

LABORATORY TEST FINDINGS

Laboratory Assay of Coagulation Parameters, Fibrinolysis and Complement Systems: Effect of iopromide on coagulation factors in *in vitro* assays increased with the administered dose. Coagulation, fibrinolysis and complement activation were evaluated with standard citrated human plasma in the following assays: Thrombin time, thrombin coagulase time, euglobulin lysis, thromboplastin time, partial thromboplastin time, plasminogen, thrombin, alpha-2 antipainasin and factor XIII activity. Thrombin inhibition was almost complete. Data on reversibility are not available. The thrombin time increased from approximately 20 seconds at an iopromide concentration of 10 mg/mL, up to 100 seconds at an iopromide concentration of 70 mg/mL.

The PTT increased from approximately 50 seconds at an 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 related renal impairment. Patients should be adequately hydrated prior to and following the intravascular administration of iodinated contrast agents. Dose adjustments in renal impairment have not been studied. (See **DRUG INTERACTIONS**.)

INTRA-ARTERIAL: ULTRAVIST® Injection (150 mg/mL) is indicated for intra-arterial digital subtraction angiography (IA-DSA). ULTRAVIST® Injection (300 mg/mL) is indicated for cerebral arteriography and peripheral arteriography. ULTRAVIST® Injection (370 mg/mL) is indicated for coronary arteriography and left ventriculography, visceral angiography, and aortography.

INTRAVENOUS: ULTRAVIST® Injection (240 mg/mL) is indicated for peripheral venography. ULTRAVIST® Injection (300 mg/mL) is indicated for contrast enhanced computed tomographic (CECT) imaging of the head and body, and excretory urography.

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In these pediatric patients, a concentration of 300 mg/mL was employed for intravenous CECT or excretory urography. A concentration of 370 mg/mL was employed for intra-arterial and intracardiac administration in the radiographic evaluation of the heart cavities and major arteries. Most pediatric patients received initial volumes of 1–2 mL/kg.

Optimal doses of ULTRAVIST® Injection 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 on the basis of immature renal function has not been established.

ADVERSE REACTIONS

For demographics, see **CLINICAL TRIALS** section.

The following table of incidence of reactions is based upon controlled clinical trials in which ULTRAVIST® Injection was compared with nonionic contrast agents (iohexol, iopamidol, ioversol) in 1367 patients. This listing includes all reported adverse reactions regardless of attribution.

Adverse reactions are listed by body system and in decreasing order of occurrence greater than 0.5% in the iopromide group.

Body System	Adverse Experience	Iopromide		Comparators	
		No.	%	Profile No.	%
Body as a Whole	Injection site hemorrhage	23	3.2	13	2.0
	Back pain	22	3.1	16	2.4
	Pain	12	1.6	11	1.6