# Ultravist®

(brand of iopromide) Injection

| |
|---|
| 240 |
| 300 |
| 370 |

**NOT FOR INTRATHECAL USE**

**PHARMACY BULK PACKAGE**
**NOT FOR DIRECT INFUSION**

**ULTRAVIST® Injection 240 mgI/mL Pharmacy Bulk Package**

**ULTRAVIST® Injection 300 mgI/mL Pharmacy Bulk Package**

**ULTRAVIST® Injection 370 mgI/mL Pharmacy Bulk Package**

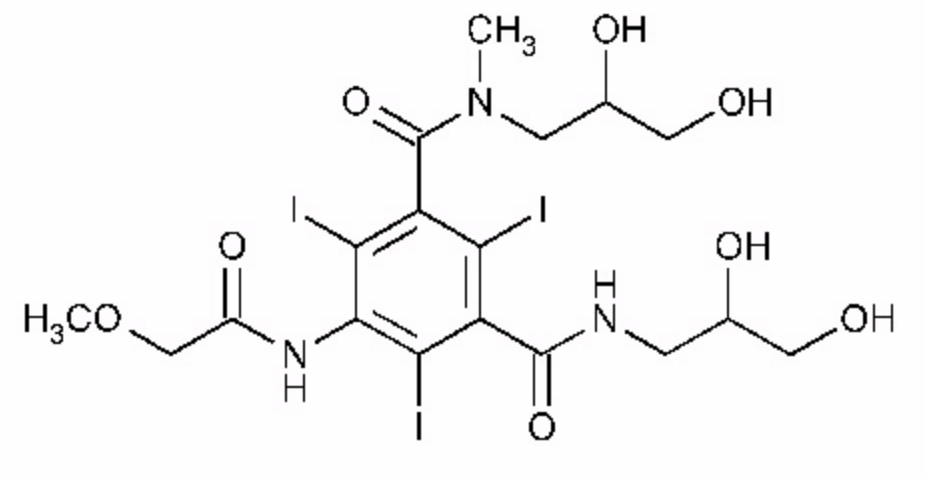
**Nonionic contrast agents**

**Rx Only**

## DESCRIPTION

ULTRAVIST® (iopromide) Injection is a nonionic, water soluble x-ray contrast agent for intravascular administration. Each bottle is to be used as a Pharmacy Bulk Package for dispensing multiple single dose preparations utilizing a suitable transfer device. The chemical name for iopromide is 1,3-Benzenedicarboxamide, *N*,*N*'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methyl-. 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. ULTRAVIST® Injection Pharmacy Bulk Package is available in three strengths: ULTRAVIST® Injection 240 mgI/mL, ULTRAVIST® Injection 300 mgI/mL and ULTRAVIST® Injection 370 mgI/mL.

Each mL of ULTRAVIST® Injection 240 mgI/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 mgI/mL Pharmacy Bulk Package provides 623.40 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 370 mgI/mL Pharmacy Bulk Package 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 (mgI/mL) available have the following physicochemical properties:

| PROPERTY | ULTRAVIST® Injection 240 mgI/mL | ULTRAVIST® Injection 300 mgI/mL | ULTRAVIST® Injection 370 mgI/mL |
|---|---|---|---|
| Osmolality* (mOsmol/kg water) @37°C | 483 | 607 | 774 |
| Osmolarity* (mOsmol/L) @37°C | 368 | 428 | 496 |
| Viscosity (cP) @20°C<br>@37°C | 4.9<br>2.8 | 9.2<br>4.9 | 22.0<br>10.0 |
| Density (g/mL) @20°C<br>@37°C | 1.262<br>1.255 | 1.330<br>1.322 | 1.409<br>1.399 |

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

Solutions of ULTRAVIST® Injection 240 mgI/mL, 300 mgI/mL and 370 mgI/mL have osmolalities from approximately 1.7 to 2.7 times that of plasma (285 mOsmol/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 hemodilution occurs.

**Pharmacokinetics**

In healthy young male volunteers receiving ULTRAVIST® Injection intravenously in doses corresponding to 15.0 or 80.0 g iodine, the pharmacokinetics are dose proportionate and first order. The compound is predominantly distributed in the extracellular space as suggested by a steady-state volume of distribution of 16 L. Iopromide's plasma protein binding is 1% and negligible. The mean total and renal clearances are 107 $mL \bullet min^{-1}$ and 104 $mL \bullet min^{-1}$, respectively. After an initial fast distribution phase with a half-life of 0.24 hour, a main elimination phase with a half-life of 2.0 hours and a slower terminal elimination phase with a half-life of 6.2 hours can be 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 ratio of the renal clearance 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 receiving ULTRAVIST® Injection in doses 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 and renal clearances are between 81-125 $mL \bullet min^{-1}$ and 70-115 $mL \bullet min^{-1}$ respectively in these patients, and are similar to the values found in the young volunteers. The distribution phase 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 protein.

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 systemically 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 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 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 osmolar, nonionic iodinated contrast media, were administered to 659 patients. Of patients given ULTRAVIST® Injection, 1 patient was less than 18 years of age, 347 patients were between 18 and 59 years of age, and 360 patients were equal to or greater than 60 years of age; the mean age was 56.6 years (range 17 - 88). Of the 708 patients, 446 (63%) were male and 262 (37%) were female. The racial distribution was: Caucasian 463 (65.4%), Black 95 (13.4%) , Hispanic 36 (5.1%) , Asian 11 (1.6 %), and other or unknown 103 (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, and 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 studied with 1 of 4 concentrations (370 mgI/mL, 300 mgI/mL, 240 mgI/mL, and 150 mgI/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 mgI/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 mgI/mL and 43 with iopamidol 300 mgI/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

mgI/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 mgI/mL and 21 with iopamidol 370 mgI/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 mgI/mL, 44 with iohexol 350 mgI/mL and 33 with iopamidol 370 mgI/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 radiologic findings by other diagnostic methods was not obtained. The risks of renal arteriography could not be analyzed.

CECT of head and body was evaluated in 3 randomized, double-blind clinical trials in patients with vascular disorders. A total of 95 patients received ULTRAVIST® Injection 300 mgI/mL, 40 received iohexol 300 mgI/mL and 55 received iopamidol 300 mgI/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 mgI/mL in patients with disorders affecting venous drainage of the limbs. Results were assessed in 63 ULTRAVIST® Injection patients, 41 patients with iohexol 240 mgI/mL and 21 with ioversol 240 mgI/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.

Similar studies were completed with comparable findings noted in intra-arterial digital subtraction angiography, peripheral arteriography and excretory urography.

**INDICATIONS AND USAGE**

INTRA-ARTERIAL:

ULTRAVIST® Injection (300 mgI/mL) is indicated for cerebral arteriography and peripheral arteriography.

ULTRAVIST® Injection (370 mgI/mL)* is indicated for coronary arteriography and left ventriculography, visceral angiography, and aortography.

INTRAVENOUS:

ULTRAVIST® Injection (240 mgI/ mL) is indicated for peripheral venography.

ULTRAVIST® Injection (300 mgI/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 **DOSAGE 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 contraindicated.

**WARNINGS**

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

Nonionic iodinated contrast 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 paraproteinacious diseases, who are prone to disease-induced renal insufficiency and/or 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 prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

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 agent.

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. 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 administered intravascularly.

**PRECAUTIONS**

**General:** THE DECISION TO USE CONTRAST ENHANCEMENT IS ASSOCIATED WITH RISK AND INCREASED RADIATION 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, 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 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 allergens, 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:* 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 the intravascular administration of iodinated contrast agents. Dose adjustments in renal impairment have not been studied. (See **DRUG INTERACTIONS**.)

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 barriers and associated renal impairment, 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.

*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 previous reaction to a contrast agent, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) other hypersensitivities, and underlying immune disorders, autoimmunity or immunodeficiencies that predispose to specific or non-specific mediator release. (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 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.

*Anesthesia:* 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 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.

*Angiography:* 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 homocystinuria 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 risk. Also, the inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast 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 (0.00066 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 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 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 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 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 withheld 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 hypersensitivity reactions, iodinated contrast 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 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 a cholecystographic 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 estimations, e.g., $T_3$ resin uptake and total or free thyroxine ($T_4$) assays are not affected.

## LABORATORY TEST FINDINGS

Laboratory Assay of Coagulation Parameters, Fibrinolysis and Complement System:

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, calcium thromboplastin time, partial thromboplastin time, plasminogen, thrombin, alpha-2 antiplasmin and factor XIIa 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 mgI/mL, up to 100 seconds at an iopromide concentration of 70 mgI/mL.

The PTT increased from approximately 50 seconds at an iopromide concentration of 10 mgI/mL, up to approximately 100 seconds at an iopromide concentration of 70 mgI/mL. A similar increase was noted in the thrombin coagulase time. Lesser effects were noted in the calcium thromboplastin time. Coagulation time increased from 13.5 to 23 seconds at the highest iopromide concentration of 70 mgI/mL. The Hageman factor split products decreased by about 20 % over the range of 10 to 70 mgI/mL of iopromide. Plasminogen was relatively stable. There was no evidence of activation of fibrinolysis. The complement alternate pathway was activated. Factor B conversion increased in a dose dependent manner. The duration of these effects was not studied.

*In vitro* studies with human blood showed that iopromide had a slight effect on coagulation and fibrinolysis which was similar to that from iohexol. Measurements of partial thromboplastin time and calcium thromboplastin time showed that the anticoagulant action was slightly more marked with iopromide than with iohexol. Iopromide also inhibited thrombin activity somewhat more than iohexol. No Factor XIIa formation could be demonstrated. The complement alternate pathway also can be activated.

## CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term animal studies have not been performed with iopromide to evaluate carcinogenic potential or effects on fertility. Iopromide was not genotoxic in a series of studies including the Ames test, an *in vitro* human lymphocytes analysis of chromosomal aberrations, an *in vivo* mouse micronucleus assay, and in an *in vivo* mouse dominant lethal assay.

## PREGNANCY

Teratogenic Effects: Pregnancy Category B

Reproduction studies performed with iopromide in rats and rabbits at doses up to 3.7 gI/kg (2.2 times the maximum recommended dose for a 50 kg human, or approximately 0.7 times the human dose following normalization of the data to body surface area estimates) have revealed no evidence of direct harm to the fetus. Embryolethality was observed in rabbits that received 3.7 gI/kg, but this was considered to have been secondary to maternal toxicity. 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 ULTRAVIST® 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 potential adverse reaction, and consideration should be given to temporarily discontinuing nursing.

**PEDIATRIC USE**

The safety and efficacy of ULTRAVIST® Injection have been established in the pediatric population over 2 years of age. Use of ULTRAVIST® Injection in these age groups is supported by evidence from adequate and well controlled studies of ULTRAVIST® Injection in adults and additional safety data obtained in literature and other reports in a total of 274 pediatric patients. Of these, there were 131 children (2-12 years), 57 adolescents, and 86 children of unreported or other ages. There were 148 females, 94 males and 32 in whom gender was not reported. The racial distibution was: Caucasion 93 (33.9%), Black 1 (0.4%), Oriental 6 (2.2%), and unknown 174 (63.5%). These patients were evaluated in intra-arterial coronary angiographic (n=60), intravenous contrast enhanced computerized tomography (CECT) (n=87), excretory urography (n=99) and 28 other procedures.

In these pediatric patients, a concentration of 300 mgI/mL was employed for intravenous CECT or excretory urography. A concentration of 370 mgI/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.

| ADVERSE EVENTS REPORTED IN >0.5% OF PATIENTS WHO RECEIVED ULTRAVIST IN CLINICAL TRIALS | | | |
|---|---|---|---|
| Body System | Adverse Experience | Iopromide<br>No. % | Comparators<br>Pooled<br>No. % |
| Total Patients at Risk | | 708 | 659 |
| Body as a Whole | Injection site hemorrhage (hematoma)<br>Back pain<br>Pain<br>Injection site pain | 23 3.2<br>22 3.1<br>13 1.8<br>9 1.3 | 13 2.0<br>16 2.4<br>12 1.8<br>3 0.5 |
| Cardiovascular | Vasodilatation<br>Chest pain<br>Hypertension<br>Hypotension | 30 4.2<br>18 2.5<br>8 1.1<br>6 0.8 | 22 3.3<br>16 2.4<br>10 1.5<br>11 1.7 |
| Digestive | Nausea<br>Vomiting<br>Nausea & vomiting<br>Tenesmus | 28 4.0<br>13 1.8<br>7 1.0<br>6 0.8 | 31 4.7<br>11 1.7<br>10 1.5<br>4 0.6 |
| Nervous | Headache<br>Dizziness<br>Somnolence<br>Confusion<br>Paresthesia | 43 6.1<br>9 1.3<br>6 0.8<br>5 0.7<br>5 0.7 | 39 5.9<br>7 1.1<br>5 0.8<br>2 0.3<br>3 0.5 |
| Respiratory | Dyspnea | 4 0.6 | 5 0.8 |
| Skin | Urticaria | 5 0.7 | 2 0.3 |
| Special Senses | Abnormal vision<br>Taste perversion | 12 1.7<br>10 1.4 | 15 2.3<br>4 0.6 |
| Urogenital | Urinary urgency | 21 3.0 | 11 1.7 |

| ADVERSE EVENTS REPORTED IN >0.5% OF PATIENTS WHO RECEIVED ULTRAVIST IN CLINICAL TRIALS | | | |
|---|---|---|---|
| Body System | Adverse Experience | Iopromide No. % | Comparators Pooled No. % |
| | Dysuria | 6 0.8 | 1 0.2 |
| | Urinary Retention | 4 0.6 | 7 1.1 |

One or more adverse reactions were recorded in 229 of 708 (32%) patients during the clinical trials, coincidental with the administration of ULTRAVIST® Injection or within the defined duration of the study follow-up period (24 - 72 hours). The incidence and type of adverse reactions were similar to those of the studied nonionic comparators (iohexol, iopamidol, ioversol) used in the clinical trials. Also, as with other contrast agents, ULTRAVIST® Injection is often associated with sensations of warmth and/or pain. The incidence is similar to the other nonionic contrast comparators.

Serious, life-threatening and fatal reactions have been associated with the administration of iodine-containing contrast media, including ULTRAVIST® Injection. In clinical trials 7/708 patients given ULTRAVIST® Injection and 4/659 given a comparator died 5 days or later after drug administration. Also, 8/708 patients given ULTRAVIST® Injection and 4/659 given a comparator had serious adverse events. Rare reports of death due to anaphylaxis and thrombosis have been documented during foreign postmarketing surveillance.

The following adverse reactions were observed in ≤ 0.5% of the subjects receiving ULTRAVIST® Injection:

BODY: abdominal pain, asthenia, chills, dry mouth, edema of the face, fever, malaise, neck pain; CARDIOVASCULAR: AV block (complete), bradycardia, coronary thrombosis, hypoxia, peripheral vascular disorder, pulmonary hypertension, sweating increase, syncope, vascular anomaly, ventricular extrasystoles; DIGESTIVE: constipation, diarrhea, dyspepsia, salivation increase, sore throat; INJECTION SITE REACTIONS: edema, erythema, rash; METABOLIC: excessive thirst; MUSCULOSKELETAL: arthralgia, myasthenia; NERVOUS SYSTEM: agitation, anxiety; convulsion, depression, emotional lability, hypertonia, hypesthesia, incoordination, insomnia, neuropathy, speech disorder, tremor; RESPIRATORY: apnea, asthma, cough increased, pharyngitis, respiratory disorder (unspecified); SKIN AND APPENDAGES: pruritus, rash; SPECIAL SENSES: visual field defect; UROGENITAL: dysmenorrhea, kidney pain.

Additional adverse events reported in foreign postmarketing surveillance and other trials with the use of ULTRAVIST® Injection include: apparent hypersensitivity reactions, congestive heart failure, tachycardia, ventricular fibrillation, hemopericardium, aphasia, tongue paralysis, amnesia, hypotonia, mydriasis, lacrimation disorder, hematuria, renal failure, and skin discoloration.

*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. Additional adverse reactions reported in pediatric patients from foreign marketing surveillance or other information are: epistaxis, angioedema, migraine, joint disorder (effusion), muscle cramps, mucous membrane disorder (mucosal swelling), conjunctivitis, hypoxia, fixed eruptions, vertigo, diabetes insipidus, and brain edema.

**OVERDOSAGE**

The adverse effects of overdosage are 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.

ULTRAVIST® Injection binds negligibly to plasma or serum protein and can, therefore, be dialyzed.

**DOSAGE AND ADMINISTRATION - General**

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

The combination of volume and concentration of ULTRAVIST® Injection 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. Specific dose adjustments for age, gender, weight and renal function have not been studied for ULTRAVIST® Injection. As with all iodinated contrast agents, lower doses may have less risk. The efficacy of ULTRAVIST® Injection below doses recommended has not been studied. 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 in adults is 86 grams.

If, during administration, an adverse reaction occurs, the injection should be immediately stopped. The safety and efficacy relationships of other doses, concentrations or procedures has not been established. (See **CLINICAL PHARMACOLOGY – Pharmacokinetics** and **PEDIATRIC USE** sections.)

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

**INTRA-ARTERIAL PROCEDURES**

**Cerebral Arteriography:** ULTRAVIST® Injection (300 mgI/mL) is indicated for intra-arterial injection in the radiographic contrast evaluation of arterial lesions of the brain.

The usual individual volume for visualization of the carotid arteries ranges from 3-12 mL and for the vertebral arteries 4-12 mL. Aortic arch injection for a simultaneous four vessel study generally requires 20-50 mL.

Total dose for the procedure should not usually exceed 150 mL.

**Coronary Arteriography and Left Ventriculography:** ULTRAVIST® Injection (370 mgI/mL) is indicated for intra-arterial injection in the radiographic contrast evaluation of coronary arteries and the left ventricle. Injection rates should be approximately equal to the flow rate in the vessel being injected.

The usual individual injection volumes for visualization of the coronary arteries and left ventricle are:

| | |
|---|---|
| left coronary | range 3-14 mL |
| right coronary | range 3-14 mL |
| left ventricle | range 30-60 mL |

Total dose for the procedure should not usually exceed 225 mL.

When large individual volumes are administered, as in ventriculography and aortography, it is recommended that sufficient time be permitted to elapse between each injection to allow for subsidence of possible hemodynamic disturbances.

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.

**Aortography and Visceral Angiography:** ULTRAVIST® Injection (370 mgI/mL) is indicated for intra-arterial injection in the radiographic contrast evaluation of the aorta and major visceral arterial branches. The volume and rate of contrast injection should be proportional to the blood flow through the vessels of interest, and related to the vascular and pathological characteristics of the specific vessels being studied.

Total dose for the procedure should not usually exceed 225 mL.

**Peripheral Arteriography:** ULTRAVIST® Injection (300 mgI/mL) is indicated for intra-arterial injection in the radiographic contrast evaluation of peripheral arteries. Injection rates should be approximately equal to the flow rate in the vessel being injected.

The usual individual injection volumes for visualization of various peripheral arteries are as follows:

| | |
|---|---|
| Subclavian or femoral artery | range 5-40 mL |
| Aortic bifurcation for distal runoff | range 25-50 mL |

Total dose for the procedure should not usually exceed 250 mL.

Pulsation should be present in the artery to be injected.

**INTRAVENOUS PROCEDURES**

**Excretory Urography:** ULTRAVIST® Injection (300 mgI/mL) is indicated for intravenous injection for routine excretory urography. A volume of contrast agent which gives a dose of approximately 300 mgI per kg body weight is recommended as suitable for adults with normal renal function.

Total dose for the procedure should not usually exceed 100 mL.

**Peripheral Venography**: ULTRAVIST® Injection (240 mgI/ mL) is indicated for intravenous injection in the radiographic contrast evaluation of peripheral veins. The minimum volume necessary to visualize satisfactorily the structures under examination should be used.

Total dose for the procedure should not usually exceed 250 mL.

**Contrast Enhanced Computed Tomography (CECT):** Intravenous administration of ULTRAVIST® Injection (300 mgI/mL) is indicated for contrast enhancement in the evaluation of neoplastic and non-neoplastic lesions of the head and body (intrathoracic, intra-abdominal and retroperitoneal regions).

CECT of the Head: The usual dosage is 50-200 mL of ULTRAVIST® Injection (300 mgI/mL). Scanning may be performed immediately after completion of the intravenous administration.

Total dose for the procedure should not usually exceed 200 mL.

CECT of the Body: ULTRAVIST® Injection 300 mgI/mL may be administered intravenously by bolus injection, by rapid infusion, or by a combination of both. The usual dose for bolus injection is 50-200 mL. The usual dose for infusion is 100-200 mL.

Total dose for the procedure should not usually exceed 200 mL.

**PEDIATRIC DOSING:**

For demographics, see **PEDIATRIC USE** section.

The recommended dose in children over 2 years of age for the following evaluations is:

Cardiac chambers and related arteries:
ULTRAVIST® Injection 370 mgI/mL as 1 to 2 milliliters per kilogram (mL/kg). The maximum dose of ULTRAVIST® Injection should not exceed 4 mL/kg.

Contrast Enhanced Computerized Tomography or Excretory Urography:
ULTRAVIST® Injection 300 mgI/mL as 1 to 2 mL/kg. The maximum dose of ULTRAVIST® Injection should not exceed 3 mL/kg.

The safety and efficacy relationships of other doses, concentrations or procedures has not been established. (See **CLINICAL PHARMACOLOGY – Pharmacokinetics** and **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, ULTRAVIST® 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 vascular injections involving contrast agents.

Intravascularly administered iodinated contrast agents should be at or close to body temperature when injected.

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 condition.

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.

**Directions for Proper Use of ULTRAVIST® Injection PHARMACY BULK PACKAGE**

1. The transfering of ULTRAVIST® Injection from the PHARMACY BULK PACKAGE should be performed in a suitable work area, such as a laminar flow hood, utilizing aseptic technique.

2. The container closure may be penetrated only one time, utilizing a suitable transfer device.

3. After initial puncture the contents of the Pharmacy Bulk Package should be used within 10 hours.

4. Any unused ULTRAVIST® Injection must be discarded 10 hours after the initial puncture of the bulk package.

## HOW SUPPLIED

ULTRAVIST® Injection is a sterile, clear, colorless to slightly yellow, odorless, pyrogen-free aqueous solution. ULTRAVIST® Injection Pharmacy Bulk Package is available in three strengths.

**ULTRAVIST® Injection 240 mgI/mL Pharmacy Bulk Package**

| | |
|---|---|
| 10 x 200 mL fill/250 mL bottles | 50419-342-21 |

**ULTRAVIST® Injection 300 mgI/mL Pharmacy Bulk Package**

| | |
|---|---|
| 10 x 200 mL fill/250 mL bottles | 50419-344-21 |
| 1 x 500 mL bottles | 50419-344-50 |
| 8 x 500 mL bottles | 50419-344-58 |

**ULTRAVIST® Injection 370 mgI/mL Pharmacy Bulk Package**

| | |
|---|---|
| 10 x 250 mL bottles | 50419-346-25 |
| 1 x 500 mL bottles | 50419-346-50 |
| 8 x 500 mL bottles | 50419-346-58 |

## STORAGE

The preparation should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) and protected from light.

Mfd. for:

Berlex

Montville, New Jersey 07045

Mfd. In: Germany

USA/Berlex 6052602 3189743 3/04