

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ULTRAVIST Injection safely and effectively. See full prescribing information for ULTRAVIST Injection.

ULTRAVIST (iopromide) Injection, for intravenous or intra-arterial use
Initial U.S. Approval: 1995
PHARMACY BULK PACKAGE
NOT FOR DIRECT INFUSION

WARNING: NOT FOR INTRATHECAL USE
Inadvertent intrathecal administration may cause death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema.

-----RECENT MAJOR CHANGES-----

Boxed Warning 12/2009
Indications and Usage (1.2) 12/2009
Dosage and Administration (2.2) 12/2009
Contraindications (4) 12/2009

-----INDICATIONS AND USAGE-----

ULTRAVIST (iopromide) Injection is a radiographic contrast agent indicated for:

- Cerebral arteriography and peripheral arteriography (300 mg I/mL) (1.1)
- Coronary arteriography and left ventriculography, visceral angiography and aortography (370 mg I/mL) (1.1)
- Peripheral venography (240 mg I/mL) (1.2)
- Contrast computed tomography (CT) imaging of head and body (300 mg I/mL and 370 mg I/mL) (1.2)
- Excretory urography (300 mg I/mL) (1.2)

-----DOSAGE AND ADMINISTRATION-----

Carefully individualize the volume and concentration of ULTRAVIST Injection to be used for a vascular procedure, according to the specific dosing tables. Adjust the dose accounting for factors such as age, body weight, size of the vessel and the rate of blood flow within the vessel. (2)

-----DOSAGE FORMS AND STRENGTHS-----

ULTRAVIST Injection PHARMACY BULK PACKAGE is available in three strengths: 240 mg I/mL; 300 mg I/mL; 370 mg I/mL. (3)

-----CONTRAINDICATIONS-----

- ULTRAVIST Injection is contraindicated for intrathecal use. (4)
- Preparatory dehydration (for example, prolonged fasting and the administration of a laxative before ULTRAVIST Injection) is

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: NOT FOR INTRATHECAL USE

1 INDICATIONS AND USAGE

- 1.1 Intra-Arterial Procedures
- 1.2 Intravenous Procedures

2 DOSAGE AND ADMINISTRATION

- 2.1 Intra-Arterial Procedures
- 2.2 Intravenous Procedures
- 2.3 Pediatric Dosing

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Anaphylactoid Reactions
- 5.2 Acute Renal Failure
- 5.3 Cardiovascular Reactions
- 5.4 Thromboembolic Complications
- 5.5 Reactions in Patients with Hyperthyroidism, Pheochromocytoma, or Sickle Cell Disease
- 5.6 Extravasation
- 5.7 Increased Radiation Exposure
- 5.8 Interference with Image Interpretation

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

contraindicated in pediatric patients because of risk of renal failure. (4)

-----WARNINGS AND PRECAUTIONS-----

- **Anaphylactoid Reactions:** Life-threatening or fatal anaphylactoid reactions may occur during or after ULTRAVIST administration, particularly in patients with allergic disorders. (5.1)
- **Acute Renal Failure:** Acute renal failure may occur following ULTRAVIST administration, particularly in patients with renal insufficiency, diabetes, multiple myeloma. Exercise caution and use the lowest necessary dose of ULTRAVIST in patients with renal dysfunction. (5.2)
- **Cardiovascular Reactions:** Hemodynamic disturbances including shock and cardiac arrest may occur during or shortly after administration of ULTRAVIST.(5.3)
- **Thromboembolic Complications:** Angiography may be associated with local and distal organ damage, ischemia, thromboembolism and organ failure. In angiographic procedures, consider the possibility of dislodging plaques or damaging or perforating the vessel wall. The physicochemical properties of the contrast agent, the dose and the speed of injection can influence the reactions. (5.4)

-----ADVERSE REACTIONS-----

Most common adverse reactions (>1%) are headache, dysgeusia, abnormal vision, chest pain, vasodilatation, nausea, vomiting, back pain, urinary urgency, injection site and infusion site reactions, and pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Do not mix other drugs with ULTRAVIST Injection. (7)
- Stop biguanides (for example, metformin) 48 hours before the contrast medium examination and withhold 48 hours after the procedure. (7)

-----USE IN SPECIFIC POPULATIONS-----

- 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. (8.1)
- The safety and efficacy of ULTRAVIST Injection have been established in the pediatric population over 2 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2009

6.3 Pediatrics

7 DRUG INTERACTIONS

- 7.1 Drug-Drug Interactions
- 7.2 Drug-Laboratory Test Interactions

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. [see *Contraindications (4)*.]

1 INDICATIONS AND USAGE

ULTRAVIST[®] Injection is an iodinated contrast agent indicated for:

1.1 Intra-Arterial Procedures*

- 300 mg I/mL for cerebral arteriography and peripheral arteriography
- 370 mg I/mL for coronary arteriography and left ventriculography, visceral angiography, and aortography

1.2 Intravenous Procedures*

- 240 mg I/mL for peripheral venography
- 300 mg I/mL for excretory urography
- 300 mg I/mL and 370 mg I/mL for contrast Computed Tomography (CT) of the head and body (intrathoracic, intra-abdominal and retroperitoneal regions) for the evaluation of neoplastic and non-neoplastic lesions. The usefulness of contrast enhancement for the investigation of the retrobulbar space and of low grade or infiltrative glioma has not been demonstrated

*For information on the concentrations and doses for the Pediatric Population [see *Dosage and Administration (2.3)* and *Use in Specific Populations (8.4)*].

2 DOSAGE AND ADMINISTRATION

- Visually inspect ULTRAVIST for particulate matter and/or discoloration, whenever solution and container permit. Do not administer ULTRAVIST if particulate matter and/or discoloration is observed.
- Determine the volume and concentration of ULTRAVIST Injection to be used taking into account factors such as age, body weight, size of the vessel and the rate of blood flow within the vessel; consider also extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed. 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 established.
- The maximum recommended total dose of iodine in adults is 86 grams; a maximum recommended total dose of iodine has not been established for pediatric patients.
- Hydrate patients adequately prior to and following the intravascular administration of ULTRAVIST. [see *Warnings and Precautions (5.2)*.]

2.1 Intra-Arterial Procedures

The volume and rate of injection of the contrast agent will vary depending on the injection site and the area being examined. Inject contrast at rates approximately equal to the flow rate in the vessel being injected.

- *Cerebral Arteriography (300 mg I/mL), Coronary Arteriography and Left Ventriculography (370 mg I/mL), Peripheral Arteriography (300 mg I/mL):* see **Table 1**.
- *Aortography and Visceral Angiography (370 mg I/mL):*

Use a volume and rate of contrast injection proportional to the blood flow and related to the vascular and pathological characteristics of the specific vessels being studied. Do not exceed 225 mL as total dose for the procedure.

		Cerebral Arteriography (300 mg I/mL)	Peripheral Arteriography (300 mg I/mL)	Coronary Arteriography and Left Ventriculography (370 mg I/mL)
Intra-Arterial Injection Sites	Carotid Arteries	3–12 mL	-	-
	Vertebral Arteries	4–12 mL	-	-
	Aortic Arch Injection (4 vessel study)	20–50 mL	-	-
	Right Coronary Artery	-	-	3–14 mL
	Left Coronary Artery	-	-	3–14 mL
	Left Ventricle	-	-	30–60 mL
	Subclavian or Femoral Artery	-	5–40 mL	-
	Aortic Bifurcation (distal runoff)	-	25–50 mL	-
	Maximum Total Dose	150 mL	250 mL	225 mL

2.2 Intravenous Procedures

- *Peripheral Venography (240 mg I/mL):*

Inject the minimum volume necessary to visualize satisfactorily the structures under examination. Do not exceed 250 mL as total dose for the procedure.

- *Contrast Computed Tomography (CT) (300 mg I/mL and 370 mg I/mL) and Excretory Urography (300 mg I/mL):* see **Table 2.**

	Excretory Urography (300 mg I/mL)	Contrast Computed Tomography (300 mg I/mL)	Contrast Computed Tomography (370 mg I/mL)
Excretory Urography	Approximately 300 mg I/kg body wt. (Adults with normal renal function)	-	-
Head	-	50–200 mL	41–162 mL
<u>Body:</u> Bolus Injection	-	50–200 mL	41–162 mL
Rapid Infusion	-	100–200 mL	81–162 mL
Maximum Total Dose	100 mL	200 mL (60 g iodine)	162 mL (60 g iodine)

2.3 Pediatric Dosing

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

- Intra-arterial:

Cardiac chambers and related arteries (370 mg I/mL):

Inject 1 to 2 milliliters per kilogram (mL/kg). Do not exceed 4 mL/kg as total dose.

- Intravenous:

Contrast Computerized Tomography or Excretory Urography (300 mg I/mL):

Inject 1 to 2 mL/kg. Do not exceed 3 mL/kg as total dose.

The safety and efficacy relationships of other doses, concentrations or procedures have not been established [see *Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

ULTRAVIST Injection is a nonionic, sterile, clear, colorless to slightly yellow, odorless, pyrogen-free aqueous solution of iopromide, containing 2.42 mg/mL tromethamine buffer and 0.1 mg/mL edetate calcium disodium stabilizer.

ULTRAVIST Injection PHARMACY BULK PACKAGE is available in three strengths:

240 mg I/mL provides 498.72 mg/mL iopromide,

300 mg I/mL provides 623.4 mg/mL iopromide,

370 mg I/mL provides 768.86 mg/mL iopromide.

4 CONTRAINDICATIONS

- Do not administer ULTRAVIST Injection intrathecally. Inadvertent intrathecal administration may cause death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema.
- Preparatory dehydration (for example, prolonged fasting and the administration of a laxative) before ULTRAVIST Injection is contraindicated in pediatric patients because of risk of acute renal failure.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylactoid Reactions

Life-threatening or fatal, anaphylactoid reactions, may occur during or after ULTRAVIST administration. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Increased risk is associated with a history of previous reaction to a contrast agent (3-fold), a known sensitivity to iodine and known allergic disorders (that is, bronchial asthma, hay fever and food allergies) or other hypersensitivities (2-fold) [see *Drug Interactions (7.1)*]. Exercise extreme caution when considering the use of iodinated contrast agents in patients with these histories or disorders.

Emergency facilities and personnel trained in the treatment of anaphylactoid reactions should be available for at least 30 to 60 minutes after ULTRAVIST administration.

5.2 Acute Renal Failure

Acute renal insufficiency or failure may occur following ULTRAVIST administration, particularly in patients with advanced vascular disease, congestive heart disease, diabetes, multiple myeloma or other paraproteinacious diseases, patients on medications which alter renal function and the elderly with age-related renal impairment. ULTRAVIST is cleared by glomerular filtration; patients with renal insufficiency have increased systemic exposure to ULTRAVIST as compared to patients with normal renal function [see *Use in Specific Populations (8.6)*].

Exercise caution and use the lowest necessary dose of ULTRAVIST in patients with renal insufficiency. Adequately hydrate patients prior to and following ULTRAVIST administration. 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. Observe such patients for several hours following the procedure to detect delayed hemodynamic renal function disturbances.

5.3 Cardiovascular Reactions

The increase in the circulatory osmotic load may induce acute or delayed hemodynamic disturbances in patients with congestive heart failure, severely impaired renal function, combined renal and hepatic disease, combined renal and cardiac disease, particularly when repetitive and/or large doses are administered [see *Drug Interactions (7)*].

Among patients who have had cardiovascular reactions, most deaths occurred from the start of injection to 10 minutes later; the main feature was cardiac arrest with cardiovascular disease as the main underlying factor. Isolated reports of hypotensive collapse and shock have been published.

Based upon published reports, deaths from the administration of iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent). Observe patients with preexisting cardiovascular disease for several hours following ULTRAVIST administration.

5.4 Thromboembolic Complications

- Angiography may be associated with local and distal organ damage, ischemia, thromboembolism and organ failure including stroke, brachial plexus palsy, chest pain, myocardial infarction, sinus arrest, hepato-renal function abnormalities. For these reasons, meticulous angiographic techniques are recommended, including close attention to guide wire 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. In angiographic procedures, consider the possibility of dislodging plaques or damaging or perforating the vessel wall with resultant pseudoaneurysms, hemorrhage at puncture site, dissection of coronary artery during catheter manipulations and contrast agent injection. The physicochemical properties of the contrast agent, the dose and the speed of injection can influence the reactions. Test injections to ensure proper catheter placement are suggested. Increased thrombosis and activation of the complement system has also occurred. Specialized personnel, and adequate equipment and facilities for immediate resuscitation and cardioversion are necessary. Monitor electrocardiograms and vital signs throughout the procedure.
- Clotting may occur when blood remains in contact with syringes containing iodinated contrast agents.
- Avoid angiography whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism [see *Clinical Pharmacology* (12.2)].

5.5 Reactions in Patients with Hyperthyroidism, Pheochromocytoma, or Sickle Cell Disease

Thyroid storm in patients with hyperthyroidism. Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule. Evaluate the risk in such patients before use of any iodinated contrast agent.

Hypertensive crises in patients with pheochromocytoma. Administer iodinated contrast agents with extreme caution in patients with known or suspected of having pheochromocytoma. Inject the minimum amount of contrast necessary. Assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.

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

5.6 Extravasation

Extravasation of ULTRAVIST Injection may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease.

5.7 Increased Radiation Exposure

The decision to use contrast enhancement is associated with risk and increased radiation exposure. Use contrast after a careful evaluation of clinical, other radiologic data, and the results of non-contrast CT findings, taking into account the increased radiation dose and other risks.

5.8 Interference with Image Interpretation

As with other iodinated contrast agents, the use of ULTRAVIST Injection may obscure some lesions which were seen on non-contrast CT scans.

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. However, older infarctions may be obscured by the contrast agent.

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. Accumulation of contrast in the brain also occurs in patients where the blood-brain barrier is known or suspected to be disrupted.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

Bayer Response NDA 021425 Ultravist PBP 04 Jun 10

The following table of incidence of reactions is based upon controlled clinical trials in which ULTRAVIST Injection was administered to 1142 patients. This listing includes all reported adverse reactions regardless of attribution.

Adverse reactions are listed by System Organ Class and in decreasing order of occurrence for rates greater than 1% in the ULTRAVIST group.

Table 3: ADVERSE REACTIONS REPORTED IN > 1% OF PATIENTS WHO RECEIVED ULTRAVIST INJECTION IN CLINICAL TRIALS		
System Organ Class	Adverse Reaction	ULTRAVIST Injection
		N=1142 (%)
Nervous system disorders	Headache	46 (4)
	Dysgeusia	15 (1.3)
Eye disorders	Abnormal Vision	12 (1.1)
Cardiac disorders	Chest pain	18 (1.6)
Vascular disorders	Vasodilatation	30 (2.6)
Gastrointestinal disorders	Nausea	42 (3.7)
	Vomiting	22 (1.9)
Musculoskeletal and connective tissue disorders	Back pain	22 (1.9)
Renal and urinary disorders	Urinary urgency	21 (1.8)
General disorders and administration site conditions	Injection site and infusion site reactions (hemorrhage, hematoma, pain, edema, erythema, rash)	41 (3.7)
	Pain	13 (1.4)

One or more adverse reactions were recorded in 273 of 1142 (24%) patients during the clinical trials, coincident with the administration of ULTRAVIST Injection or within the defined duration of the study follow-up period (24–72 hours). ULTRAVIST Injection is often associated with sensations of warmth and/or pain.

Serious, life-threatening and fatal reactions have been associated with the administration of iodine-containing contrast media, including ULTRAVIST Injection. In clinical trials 7/1142 patients given ULTRAVIST Injection died 5 days or later after drug administration. Also, 10/1142 patients given ULTRAVIST Injection had serious adverse events.

The following adverse reactions were observed in ≤1% of the subjects receiving ULTRAVIST Injection:

Cardiac disorders: atrio ventricular block (complete), bradycardia, ventricular extrasystole;

Gastrointestinal disorders: abdominal discomfort, abdominal pain, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, gastrointestinal disorder, gastrointestinal pain, salivation increased, stomach discomfort, rectal tenesmus;

General disorders and administration site conditions: asthenia, chest discomfort, chills, excessive thirst, extravasation, feeling hot, hyperhydrosis, malaise, edema peripheral, pyrexia;

Immune system disorders: asthma, face edema;

Investigations: blood lactate dehydrogenase increased, blood urea increased, hemoglobin increased, white blood cell count increased;

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain, myasthenia, neck pain, pain in extremity;

Nervous system disorders: agitation, confusion, convulsion, dizziness, hypertonia, hypesthesia, incoordination, neuropathy, somnolence, speech disorder, tremor, paresthesia, visual field defect;

Psychiatric disorders: anxiety;

Renal and urinary disorders: dysuria, renal pain, urinary retention;

Respiratory, thoracic and mediastinal disorders: apnea, cough increased, dyspnea, hypoxia, pharyngeal edema, pharyngitis, pleural effusion, pulmonary hypertension, respiratory disorder, sore throat;

Skin and subcutaneous tissue disorders: erythema, pruritus, rash, urticaria;

Vascular disorders: coronary artery thrombosis, flushing, hypertension, hypotension, peripheral vascular disorder, syncope, vascular anomaly.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ULTRAVIST Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported in foreign postmarketing surveillance and other trials with the use of ULTRAVIST Injection include:

Cardiac disorders: cardiac arrest, ventricular fibrillation, atrial fibrillation, tachycardia, palpitations, congestive heart failure, myocardial infarction, angina pectoris;

Ear and labyrinth disorders: vertigo, tinnitus;

Endocrine disorders: hyperthyroidism, thyrotoxic crisis, hypothyroidism;

Eye disorders: mydriasis, lacrimation disorder;

Gastrointestinal disorders: dysphagia, swelling of salivary glands;

Immune system disorders: anaphylactoid reaction (including fatal cases), respiratory arrest, anaphylactoid shock, angioedema, laryngeal edema, laryngospasm, bronchospasm, hypersensitivity;

Nervous system disorders: cerebral ischemia/infarction, paralysis, paresis, transient cortical blindness, aphasia, coma, unconsciousness, amnesia, hypotonia;

Renal and urinary disorders: renal failure, hematuria;

Respiratory, thoracic and mediastinal disorders: pulmonary edema, acute respiratory distress syndrome, asthma;

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome, skin discoloration;

Vascular disorders: vasospasm.

6.3 Pediatrics

The overall character, quality, and severity of adverse reactions in pediatric patients are generally similar to those reported in adult patients. 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. [see *Use in Specific Populations* (8.4).]

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

In patients taking biguanides (for example, metformin), acute alterations in renal function after iodinated contrast agents may precipitate lactic acidosis. Stop biguanides 48 hours before the contrast medium examination and withhold until 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, use caution when administering iodinated contrast agents to patients taking beta-blockers.

Interleukins are associated with an increased prevalence of delayed hypersensitivity reactions after iodinated contrast agent administration. These reactions include fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, and oliguria.

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.

Do not mix other drugs with ULTRAVIST Injection [see *How Supplied/Storage and Handling* (16)].

7.2 Drug-Laboratory Test Interactions

Thyroid Function Tests:

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, for example, T₃ resin uptake and total or free thyroxine (T₄) assays are not affected.

Laboratory Assay of Coagulation Parameters, Fibrinolysis and Complement System:

The 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 mg I/mL, up to 100 seconds at an iopromide concentration of 70 mg I/mL.

The PTT increased from approximately 50 seconds at an iopromide concentration of 10 mg I/mL, up to approximately 100 seconds at an iopromide concentration of 70 mg I/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 mg I/mL. The Hageman factor split products decreased by about 20% over the range of 10 to 70 mg I/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. No Factor XIIa formation could be demonstrated. The complement alternate pathway also can be activated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies performed with iopromide in rats and rabbits at doses up to 3.7 g I/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 g I/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.

8.3 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.

8.4 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 distribution was: Caucasian 93 (33.9%), Black 1 (0.4%), Asian 6 (2.2%), and unknown 174 (63.5%). These patients were evaluated in intra-arterial coronary angiographic (n=60), intravenous contrast computerized tomography (CT) (n=87), excretory urography (n=99) and 28 other procedures.

In these pediatric patients, a concentration of 300 mg I/mL was employed for intravenous contrast CT or excretory urography. A concentration of 370 mg I/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. In the pediatric population, the pharmacokinetic parameters have not been established.

Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent 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. Exercise caution in selecting the dose.

Safety and effectiveness in pediatric patients below the age of two have not been established.

8.5 Geriatric Use

Middle-aged and elderly patients, without significantly impaired renal function, who received ULTRAVIST Injection in doses corresponding to 9–30 g iodine, had mean steady-state volumes of distribution that ranged between 30–40 L. Mean total and renal clearances were between 81–125 mL/min and 70–115 mL/min respectively in these patients, and were similar to the values found in the young volunteers. The distribution phase half-life in this patient population was 0.1 hour, the main elimination phase half-life was 2.3 hours, and the terminal elimination phase half-life was 40 hours. The urinary excretion (97% of the dose) and fecal excretion (2%) was comparable to that observed in young healthy volunteers, suggesting that, compared to the renal route, biliary and/or gastrointestinal excretion is not significant for iopromide.

8.6 Renal Impairment

In patients with renal impairment, opacification of the calyces and pelves by iopromide may be delayed due to slower renal excretion of iopromide.

A pharmacokinetic study in patients with mild (n=2), moderate (n=6), and severe (n=3) renal impairment was conducted. The total clearance of iopromide was decreased proportionately to the baseline decrease in creatinine clearance. The plasma AUC increased about 2-fold in patients with moderate renal impairment and 6-fold in patients with severe renal impairment compared to subjects with normal renal function. The terminal half-life increased from 2.2 hrs for subjects with normal renal function to 11.6 hrs in patients with severe renal impairment. The peak plasma concentration of iopromide was not influenced by the extent of renal impairment. Exercise caution and use the lowest necessary dose of ULTRAVIST in patients with renal dysfunction [*see Warnings and Precautions (5.2)*].

10 OVERDOSAGE

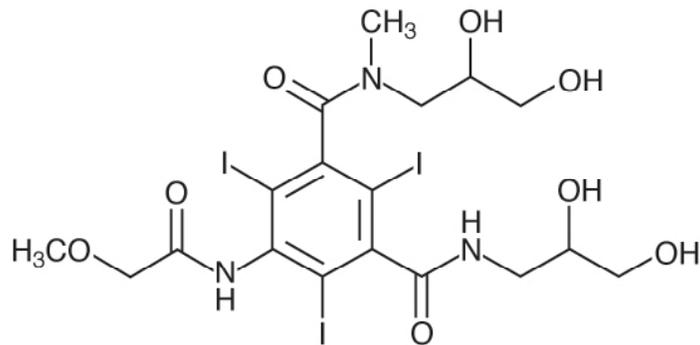
The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

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

11 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 *N,N'*-Bis(2,3-dihydroxypropyl) –2,4,6–triiodo–5–[(methoxyacetyl)amino] –*N*-methyl–1,3-benzenedicarboxamide. 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, containing 2.42 mg/mL tromethamine buffer and 0.1 mg/mL edetate calcium disodium stabilizer.

ULTRAVIST Injection Pharmacy Bulk Package is available in three strengths:

240 mg I/mL provides 498.72 mg/mL iopromide,

300 mg I/mL provides 623.4 mg/mL iopromide,

370 mg I/mL provides 768.86 mg/mL iopromide.

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) at 25± 2°C, is sterilized by autoclaving and contains no preservatives.

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

		ULTRAVIST INJECTION	ULTRAVIST INJECTION	ULTRAVIST INJECTION
Property		240 mg I/mL	300 mg I/mL	370 mg I/mL
Osmolality*(mOsmol/kg water)	@ 37°C	483	607	774
Osmolarity*(mOsmol/L)	@ 37°C	368	428	496
Viscosity (cP)	@ 20°C	4.9	9.2	22
	@ 37°C	2.8	4.9	10
Density (g/mL)	@ 20°C	1.262	1.330	1.409
	@ 37°C	1.255	1.322	1.399

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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.

12.2 Pharmacodynamics

Following ULTRAVIST administration, 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 (that is, 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.

In contrast CT, some performance characteristics are different in the brain and body. In contrast CT 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.

For information on coagulation parameters, fibrinolysis and complement system [see *Drug Interactions (7.2)*].

12.3 Pharmacokinetics

Distribution

After intravenous administration to healthy young volunteers, plasma iopromide concentration time profile shows an initial distribution phase with a half-life of 0.24 hour; a main elimination phase with a half-life of 2 hours; and a terminal elimination phase with a half-life of 6.2 hours. The total volume of distribution at steady state is about 16 L suggesting distribution in to extracellular space. Plasma protein binding of iopromide is 1%.

Iodinated contrast agents may cross the blood-brain barrier [see *Warnings and Precautions (5.8)*].

Elimination

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 iopromide. During the slower 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. Pharmacokinetics of iopromide at intravenous doses up to 80 g iodine, are dose proportionate and first order.

The mean total and renal clearances are 107 mL/min and 104 mL/min, respectively.

Metabolism

Iopromide is not metabolized.

Specific Populations

A pharmacokinetic study was conducted in 11 patients with renal impairment [see *Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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 micro-nucleus assay, and in an *in vivo* mouse dominant lethal assay.

14 CLINICAL STUDIES

ULTRAVIST Injection was administered to 708 patients; 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%). 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. Five (5) intra-arterial and three (3) intravenous procedures were studied with 1 of 4 concentrations (370 mg I/mL, 300 mg I/mL, 240 mg I/mL, and 150 mg I/mL). These procedures were: aortography/visceral angiography, coronary arteriography and left ventriculography, cerebral arteriography, peripheral arteriography, intra-arterial digital subtraction angiography (IA-DSA), contrast computed tomography (CT) of head and body, excretory urography, and peripheral venography.

Cerebral arteriography was evaluated in two randomized, double-blind clinical trials of ULTRAVIST Injection 300 mg I/mL in 80 patients with conditions such as altered cerebrovascular perfusion and/or permeability occurring in central nervous system diseases due to various CNS disorders. 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. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Coronary arteriography/left ventriculography was evaluated in two randomized, double-blind clinical trials and one unblinded, unrandomized clinical trial of ULTRAVIST Injection 370 mg I/mL in 106 patients with conditions such as altered coronary artery perfusion due to metabolic causes and in patients with conditions such as altered ventricular function. Visualization ratings were good or excellent in 99% or more of the patients a radiologic diagnosis was made in the majority of the patients. A confirmation of the radiologic findings by other diagnostic methods was not obtained.

Aortography/visceral angiography was evaluated in two randomized, double-blind clinical trials in 78 patients with conditions such as altered aortic blood flow and/or visceral vascular disorders. 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. A confirmation of radiologic findings by other diagnostic methods was not obtained. The risks of renal arteriography could not be analyzed.

Contrast CT of head and body was evaluated in three randomized, double-blind clinical trials of ULTRAVIST Injection 300 mg I/mL in 95 patients with vascular disorders. Visualization ratings were good or excellent in 99% of the patients; a radiologic diagnosis was made in the majority of the patients. A confirmation of contrast CT findings by other diagnostic methods was not obtained.

ULTRAVIST Injection was evaluated in a blinded reader trial for CT of the head and body. Among the 382 patients who were evaluated with ULTRAVIST Injection 370 mg I/mL, visualization ratings were good or excellent in approximately 97% of patients.

Peripheral venography was evaluated in two randomized, double-blind clinical trials of ULTRAVIST Injection 240 mg I/mL in 63 patients with disorders affecting venous drainage of the limbs. Visualization ratings were good or excellent in 100% of the patients; a radiologic diagnosis was made in the majority of the patients. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

ULTRAVIST Injection 240 mg I/mL Pharmacy Bulk Package

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

ULTRAVIST Injection 300 mg I/mL Pharmacy Bulk Package

Bayer Response NDA 021425 Ultravist PBP 04 Jun 10

10 x 200 mL fill/250 mL bottles 50419-344-21

8 x 500 mL bottles 50419-344-58

8 x 500 mL bottles (RFID) 50419-344-48

ULTRAVIST Injection 370 mg I/mL Pharmacy Bulk Package

10 x 250 mL bottles 50419-346-25

8 x 500 mL bottles 50419-346-58

8 x 500 mL bottles (RFID) 50419-346-48

Inspect contrast agents visually prior to use. Do not use if discolored, if particulate matter (including crystals) is present, or if containers are defective. As ULTRAVIST Injection is a highly concentrated solution, crystallization (milky-cloudy appearance and/or sediment at bottom, or floating crystals) may occur.

As with all contrast agents, because of the potential for chemical incompatibility, do not mix or inject ULTRAVIST Injection in intravenous administration lines containing other drugs, solutions or total nutritional admixtures.

Use sterile technique in all vascular injections involving contrast agents.

Inject intravascularly administered iodinated contrast agents at or close to body temperature.

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

Withdraw contrast agents from their containers under strict aseptic conditions using only sterile syringes and transfer devices. Use immediately contrast agents which have been transferred into other delivery systems.

Store the preparation at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) and protected from light.

Directions for Proper Use of ULTRAVIST Injection PHARMACY BULK PACKAGE

1. Perform the transfer of ULTRAVIST Injection from the PHARMACY BULK PACKAGE in a suitable work area, such as a laminar flow hood, utilizing aseptic technique.
2. Penetrate the container closure only one time, utilizing a suitable transfer device.
3. After initial puncture use the contents of the PHARMACY BULK PACKAGE within 10 hours.
4. Discard any unused ULTRAVIST Injection 10 hours after the initial puncture of the bulk package.

17 PATIENT COUNSELING INFORMATION

Instruct patients receiving ULTRAVIST Injection to inform their physician or healthcare provider of the following:

- if they are pregnant [see *Use in Specific Populations* (8.1)]
- if they are diabetic or if they have multiple myeloma, pheochromocytoma, homozygous sickle cell disease or thyroid disorder [see *Warnings and Precautions* (5.2, 5.5)]
- if they are allergic to any drugs or food, or if they have immune, autoimmune or immune deficiency disorders. Also, if they have had any reaction to previous injections of dyes used for x-ray procedures [see *Warnings and Precautions* (5.1)]
- all medications they are currently taking, including non-prescription (over-the-counter) drugs.

©2009, Bayer HealthCare Pharmaceuticals Inc. All rights reserved.

Mfd. for:



**Bayer HealthCare
Pharmaceuticals**

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Mfd. in Berlin, Germany

Revised 12/09