

ULTRAVIST[®]
(iopromide injection)

ULTRAVIST[®] 300
(iopromide injection 62% w/v, 300 mg I/mL)

ULTRAVIST[®] 370
(iopromide injection 77% w/v, 370 mg I/mL)

Nonionic Iodinated Radiographic Contrast Medium

For Professional Use Only

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ACTION AND CLINICAL PHARMACOLOGY

ULTRAVIST (iopromide) is a nonionic iodinated, water-soluble, radiographic contrast medium which is available in two stable, ready-to-use solutions of different concentrations. Following intravascular injection, iopromide provides radiographic opacification of the vasculature and extracellular space in the path of flow of the agent, allowing diagnostic assessment of the limbs and internal organs until significant dilution occurs. For example, after intravenous injection, opacification of the renal parenchyma begins within 1 minute. Excretion of the contrast agent becomes apparent in 1 to 3 minutes with optimal contrast in the calyces and collecting system occurring between 5 and 15 minutes. In nephropathic conditions, particularly when excretory capacity has been altered, the excretion rate varies unpredictably and opacification may be delayed for several hours after injection.

The pharmacokinetics of iopromide are similar to those of other ionic and nonionic contrast media. Immediately following intravascular injection, iopromide reaches peak plasma concentrations and is then rapidly distributed throughout the extracellular fluid compartment. It is excreted unchanged by the kidneys mainly by glomerular filtration. About 90% of the injected dose is excreted unchanged by the kidneys during the first 24 hours with peak urine concentrations occurring in the first hour. In healthy volunteers, elimination half-life is approximately 2 hours. In the dose range tested, the mean total clearance of iopromide amounts to 106 ± 12 mL/min and is similar to the renal clearance of 102 ± 15 mL/min. Thus, excretion of iopromide is almost exclusively renal. Only about 2% of the dose administered is excreted via the fecal route within 3 days.

It displays little tendency to bind to serum or plasma proteins and there is no evidence of metabolism, deiodination or biotransformation in rats and humans.

In double-blind clinical trials, ULTRAVIST has shown diagnostic efficacy comparable to other nonionic and ionic radiographic contrast agents when studied in excretory urography (vs iopamidol, ioxithalamate, and ioxaglate); renal arteriography (vs amidotrizoate) cerebral arteriography (vs iopamidol); peripheral arteriography of the leg (vs ioxaglate); phlebography of the pelvis and leg (vs ioglicinate); coronary arteriography and ventriculography (vs iohexol and diatrizoate and amidotrizoate); and in computed tomography (vs ioglicinate). In these studies ULTRAVIST has demonstrated properties comparable to other nonionic compounds with respect to neuroangiographic and cardiovascular tolerance and has demonstrated superiority over ionic agents particularly in causing less pain and warmth following injection.

The influence of iopromide on clotting, fibrinolysis, complement activation and erythrocyte morphology has been minimal (see **WARNINGS**).

INDICATIONS AND CLINICAL USE

ULTRAVIST (iopromide), provided in two strengths, is indicated for intravascular use to provide diagnostic information in a number of radiographic contrast procedures. It is also indicated for the visualization of various body cavities, eg, arthrography and hysterosalpingography.

ULTRAVIST 300	Computed tomography (CT)
	Excretory urography
	Pediatric excretory urography
	Renal arteriography
	Peripheral arteriography (bifemoral pelvis/leg)
	Cerebral arteriography
	Phlebography of the extremities
	Arthrography
ULTRAVIST 370	Computed tomography (CT)
	Excretory urography
	Coronary arteriography (including PTCA), with or without left ventriculography
	Pediatric angiocardiology
	Arthrography

CONTRAINDICATIONS

ULTRAVIST (iopromide) is not indicated for use in myelography, cerebral ventriculography, and cisternography.

ULTRAVIST should not be administered to patients with known hypersensitivity to the drug, or with manifest hyperthyroidism.

WARNINGS

Contrast media-induced nephrotoxicity, presenting as transient impairment of renal function, may occur after intravascular ULTRAVIST administration. Patients with pre-existing renal impairment, diabetes mellitus, sepsis, hypotension, dehydration, cardiovascular disease, elderly patients, and patients with multiple myeloma, hypertension, patients on medications which alter renal function and patients with hyperuricemia, are at increased risk of this condition. Patients with both renal impairment and diabetes are at the highest risk for contrast media-induced nephrotoxicity.

ULTRAVIST should only be administered to patients with a history of renal or combined renal and hepatic impairment after careful risk/benefit assessment by the prescriber. The general health condition and co-morbidity of the patients as well as the medical need for a contrast enhanced examination should be assessed. ULTRAVIST should only be used where the benefit clearly outweighs the risk. In patients with renal impairment, postpone a new contrast medium examination until renal function returns to pre-examination levels.

Nonionic iodinated contrast media inhibit blood coagulation less than ionic contrast media. Clotting has been reported in vivo and in vitro when blood remains in contact with syringes, catheters or tubes containing nonionic contrast media. Nonionic contrast media are not suitable flush solutions.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both nonionic and ionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, number of injections, catheter and syringe material, underlying disease state, and concomitant medication may contribute to the development of thromboembolic events (see **PRECAUTIONS, Intravascular Use**).

ULTRAVIST (iopromide) has been associated with serious and fatal reactions. Therefore, clear indication and evaluation of the benefit/risk ratio for every patient should precede each examination with contrast media. Also, it is of utmost importance that adequate facilities and appropriate personnel be readily available and a course of action be planned in advance for the immediate treatment of any serious untoward reaction. Diagnostic procedures utilizing a radiopaque contrast agent should be conducted only by a physician with the requisite training and a thorough knowledge of the particular procedure to be performed. The physician must also be thoroughly familiar with the emergency treatment of all adverse effects.

PRECAUTIONS

General

As with other iodinated contrast agents, the use of ULTRAVIST (iopromide) contrast enhancement may obscure some lesions which were seen on previously unenhanced CT scans.

Because unenhanced scanning may provide adequate diagnostic information in the individual patient, the decision to employ contrast enhancement, which may be associated with risk and increased radiation exposure, should be based upon a careful evaluation of clinical, other radiological, and unenhanced CT findings. Careful optimization of contrast and radiation parameters can decrease radiation exposure.

Caution is advised in patients with cardiac and circulatory insufficiency, hypertension, pheochromocytoma, cerebral arteriosclerosis, latent hyperthyroidism, severe impairment of hepatic or renal function, pulmonary emphysema, diabetes with renal dysfunction requiring treatment, cerebral arterial spasm, bland nodular goiter, multiple myeloma or other paraproteinemias, and renal transplant.

Avoid angiography whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium-related reactions. Care should be taken to minimize the state of anxiety in such patients.

Sensitivity testing using a small test dose of contrast medium is not recommended as it has no predictive value. Furthermore, sensitivity testing itself has occasionally led to serious and even fatal hypersensitivity/anaphylactoid reactions.

Cardiovascular

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.

Hypersensitivity

Before any contrast medium is injected, the patient should be questioned for a history of allergy (eg, shellfish), sensitivity to iodine or to radiographic media, previous reaction to contrast media, and bronchial asthma, as the reported incidence of hypersensitivity/anaphylactoid reactions to contrast media (including severe reactions) are higher in patients with these conditions. However, such reactions are irregular and unpredictable in nature. ULTRAVIST can also be associated with hypersensitivity/anaphylactoid or other idiosyncratic reactions characterized by cardiovascular, respiratory, and cutaneous manifestations.

Hypersensitivity/anaphylactoid reactions ranging from mild to severe reactions including shock are possible (see **ADVERSE REACTIONS**). Most adverse reactions to contrast agents appear within 30 minutes after the start of their injection, but a delayed reaction may occur hours or days after an injection. Premedication with a corticosteroid regimen may be considered in patients with an increased risk of acute hypersensitivity/anaphylactoid reactions such as patients with a previous moderate or

severe acute reaction, or patients with asthma or an allergy requiring medical treatment. However, corticosteroids should not be mixed in the same syringe with any contrast medium because of potential chemical incompatibility. Treatment with beta-blockers or general anesthesia increases the incidence and may aggravate adverse reactions, particularly in people with asthma. Patients who experience hypersensitivity/anaphylactoid reactions while taking beta-blockers may be resistant to treatment effects of beta agonists. In the event of a severe hypersensitivity/anaphylactoid reaction, patients with cardiovascular disease are more susceptible to serious or even fatal outcomes. Due to the possibility of severe hypersensitivity/anaphylactoid reactions after administration, postprocedure observation of the patient is recommended. Preparedness for instituting emergency measures is necessary for all patients.

Renal

Renal function should be assessed before injecting ULTRAVIST. ULTRAVIST is cleared by glomerular filtration; patients with renal insufficiency have increased systemic exposure to ULTRAVIST as compared to patients with normal renal function. Exercise caution and use the lowest necessary dose of ULTRAVIST in patients with renal insufficiency. Before ULTRAVIST is administered, patients should be fully assessed and precautions must be taken in patients with renal impairment. Implementation of prevention strategies is considered to be the best approach to reducing development of contrast media-induced nephrotoxicity. Acute renal insufficiency or failure may occur following ULTRAVIST administration, particularly in patients with pre-existing renal impairment, sepsis, hypotension,

dehydration, advanced vascular disease, congestive heart disease, diabetes mellitus, multiple myeloma or other paraproteinacious diseases, patients on medications which alter renal function, and the elderly with age-related renal impairment.

Adequately hydrate patients prior to and following ULTRAVIST administration in order to minimize the risk of contrast media-induced nephrotoxicity. Patients on dialysis, if without residual renal function, may receive ULTRAVIST for radiological procedures as iodinated contrast media are cleared by the dialysis process.

Please see **DOSAGE AND ADMINISTRATION, Special Populations, Patients with renal impairment**: for additional information.

Endocrine and Metabolism

Thyroid Dysfunction

Ultravist, like all other iodinated contrast median (ICM), may induce changes in thyroid function in some patients. Transient hyperthyroidism or hypothyroidism has been reported following iodinated contrast media administration to adult and pediatric patients. Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased levels of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or even more than a month (see **ADVERSE REACTIONS**). Some patients were treated for hypothyroidism (see **PRECAUTIONS, Special Populations, Infants**:)

Assessment of thyroid function may be obscured for several weeks following the administration of ULTRAVIST.

Reports of thyroid storm after 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 appropriate patients prior to the use of ULTRAVIST.

For neonates, especially preterm infants, who have been exposed to ULTRAVIST either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function, as exposure to excess iodine may cause hypothyroidism, possibly requiring treatment.

Patients with pheochromocytoma may be at an increased risk to develop a hypertensive crisis. 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.

Hepatic/Biliary/Pancreatic

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 ULTRAVIST should be postponed in patients who have to undergo oral cholecystography.

Hematologic

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

Neurologic

ULTRAVIST should be administered intravascularly with caution in situations in which there may be a reduced seizure threshold, such as a previous history of seizures and the use of certain concomitant medication (eg, antidepressants, antipsychotics and neuroleptics). Patients with seizure history or other neurologic disorders may be at increased risk to have seizures and neurological complications in relationship to ULTRAVIST administration. Neurological complications are more frequent in cerebral angiography and related procedures.

Special attention should be paid to patients with increased intracranial pressure, disrupted blood-brain barrier (tumor, subarachnoid hemorrhage, transient ischemic attack, cerebral thrombosis, ischemia) or any condition whereby the presence of contrast material in the vessels is prolonged. Serious neurological sequelae (stroke, aphasia, cortical blindness, convulsions) may occur following intraarterial or intravascular infusion of contrast media. 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. Factors which increase blood-brain barrier permeability facilitate the passage of the contrast medium into cerebral tissue, possibly leading to CNS reactions. The benefit/risk ratio of the procedure has to be evaluated and the amount of contrast medium necessary to obtain a diagnostic picture kept to a minimum.

The administration of ULTRAVIST may aggravate the symptoms of myasthenia gravis.

Special Populations

Pregnant Women:

The safe use of ULTRAVIST during pregnancy has not been established. Therefore, it should not be used unless the benefits outweigh the risks.

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.

Nursing Women:

It is not known whether ULTRAVIST 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 reactions. If the use of ULTRAVIST is considered necessary in a nursing mother, it is suggested to discontinue breast feeding for 48 hours. (see [PRECAUTIONS, Endocrine and Metabolism](#))

Pediatrics:

Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent include pediatric patients 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 (132.6 µmol/L).

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.

Exercise caution in selecting the dose. Lower rates of injection of ULTRAVIST are recommended for use in the pediatric population.

Infants:

Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or more than a month (see **ADVERSE REACTIONS**). Hypothyroidism in infants may be harmful for growth and development, including mental development and may require treatment. Thyroid function in infants exposed to ICM should therefore be evaluated and monitored until thyroid function is normalized.

Geriatrics:

Elderly patients may present a special risk in the use of radiographic contrast media. These patients may have compromised renal and cardiac function and may be taking medication (eg, beta-blockers) which may make them more susceptible to the potentially harmful effects of procedures involving the use of contrast agents.

Please see [DOSAGE AND ADMINISTRATION, Special Populations, Elderly population \(aged 65 years and above\)](#): for additional information.

Intravascular Use

ULTRAVIST produces less circulatory osmotic load than ionic contrast agents; however, it can produce significant hemodynamic disturbances especially in patients with reduced cardiac reserve. The volume of injection should be minimized and the patient's vital signs should be continuously monitored for several hours following the procedure to detect delayed hemodynamic disturbances in these patients. Hypotension should be corrected promptly as it can lead to serious arrhythmias. Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary emphysema, pulmonary hypertension or a stenotic pulmonary vascular bed because serious hemodynamic changes may occur in these individuals. Patients with significant cardiac disease or severe coronary artery disease are at an increased risk of developing clinically relevant hemodynamic changes and arrhythmia. The intravascular injection of ULTRAVIST may precipitate pulmonary edema in patients with heart failure. Mesenteric necrosis, acute pancreatitis, renal shutdown and serious neurologic complications including spinal cord damage and hemiplegia have been reported

following inadvertent injection of a large part of the aortic dose of an ionic contrast medium directly into an aortic branch or arterial trunk.

There are inherent dangers associated with catheter manipulation, contrast medium injection and angiographic procedures. 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, and 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. Fluoroscope guidance is to be used to place the catheter. 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. The possibility of these occurrences should be borne in mind during the procedure.

For coronary arteriography and left ventriculography, specialized personnel, and adequate equipment and facilities for immediate resuscitation and cardioversion are necessary. Monitor electrocardiograms and vital signs throughout the procedure.

Exercise care when performing venography in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection, venous thrombosis or a totally obstructed venous system.

Clotting may occur when blood remains in contact with syringes containing iodinated contrast agents.

Pulsation must be present in the artery to be injected. Extreme caution is therefore advised for patients considered for angiography, particularly those suspected of having thromboangiitis obliterans (Buerger's disease), since vascular procedures may induce severe arterial spasm.

In intraarterial administration, caution is advisable in patients with suspected thrombosis, ischemic disease, local infection, a totally obstructed vascular system, or severe ischemia associated with ascending infection or advanced arteriosclerosis. With the use of conventional ionic contrast media, occasional serious neurologic complications, including paraplegia, have been reported in patients with aorto-iliac or femoral artery obstruction, abdominal compression, hypotension or hypertension, and following the injection of vasopressors.

When large individual doses are administered, an appropriate time interval should elapse between injections to allow any hemodynamic disturbances to subside.

Hemodynamic changes are likely to be more pronounced following repeated injections given in rapid succession.

Following arterial catheterization and injection, pressure hemostasis is advisable with immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture.

Drug Interactions

Drug-Drug Interactions

Interleukins are associated with an increased prevalence of delayed hypersensitivity/anaphylactoid reactions after iodinated contrast agent administration. These reactions include flu-like symptoms, fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, oliguria, and joint pain.

Biguanides (metformin): In patients with acute kidney failure or severe chronic kidney disease, biguanide elimination can be reduced leading to accumulation and the development of lactic acidosis. As the application of ULTRAVIST can lead to renal impairment or an aggravation of renal impairment, patients, especially those with prior renal impairment, treated with metformin may be at an increased risk of developing lactic acidosis. As a precaution, in patients with an eGFR < 45 mL/min/1.73m², biguanides should be discontinued 48 hours prior to non-urgent contrast injections or at the time of the contrast medium examination and withheld for 48 hours after the administration of contrast medium and reinstated only after adequate renal function remains stable (less than 25% increase compared to baseline creatinine). (see **PRECAUTIONS, Renal**)

Radioisotopes: Diagnosis and treatment of thyroid disorders with thyrotropic radioisotopes may be impeded for up to several weeks after administration of ULTRAVIST due to reduced radioisotope uptake.

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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions reported with ULTRAVIST (iopromide) have generally been less frequent than with some commonly used iodinated compounds. Adverse reactions in association with the use of iodinated contrast media are usually mild to moderate and transient in nature. However, all side effects and toxicity associated with this class of compound are possible during the use of ULTRAVIST, including severe and life-threatening reactions as well as death.

Careful patient observation for adverse reactions is recommended in the use of all contrast media. Reactions accompanying use may vary with the dosage, the technique of administration, the procedure and the underlying condition of the patient. Adverse reactions generally occur within 30 minutes after injection but some may be delayed or of long-lasting nature. These reactions include: laryngospasm, bronchospasm,

wheezing, dyspnea, and status asthmaticus; angioedema, subglottic edema and signs of airway obstruction; anaphylactic shock; cardiovascular collapse with peripheral vasodilation, hypotension, tachycardia, dyspnea, cyanosis, sweating, pallor, ventricular fibrillation and cardiac arrest; CNS stimulation or depression with agitation, convulsions, coma and death. Severe life-threatening reactions to iodinated contrast media require appropriate emergency measures.

Many life-threatening reactions begin with only mild symptoms such as nasal congestion, sneezing, watery eyes, skin erythema, or a vague sense of discomfort. It is therefore extremely important that all patients be watched closely until their symptoms have abated. The symptoms, which occur regardless of the amount of contrast medium administered and the mode of administration, can indicate incipient shock. Administration of the contrast medium must then be interrupted immediately and, if necessary, specific therapy initiated intravenously. In the case of intravenous administration, use of a flexible indwelling catheter is therefore recommended.

The most frequently observed adverse drug reactions (>4%) in patients receiving ULTRAVIST are headache, nausea, and vasodilation.

The most serious adverse drug reactions in patients receiving ULTRAVIST are anaphylactoid shock, respiratory arrest, bronchospasm, laryngeal edema, pharyngeal edema, asthma, coma, cerebral infarction, stroke, brain edema, convulsion, arrhythmia, cardiac arrest, myocardial ischemia, myocardial infarction, cardiac failure, bradycardia, cyanosis, hypotension, shock, dyspnea, pulmonary edema, respiratory insufficiency and aspiration.

Clinical Trial Adverse Drug Reactions

A clinical trial dataset of 2398 patients was used to generate the adverse drug reaction profile of ULTRAVIST prior to market authorization in Canada. The following list of adverse reactions and their incidence is based on this dataset.

The adverse drug reactions listed below are also grouped by the following denotations:

^a may be associated with injection site reaction

* life-threatening and/or fatal cases have been reported

General Disorders and Administration Site	Incidence
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Conditions	
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Warmth ^a	(slight - moderate)	36.4%
	(severe)	3.0%
Pain ^a	(slight to moderate)	6.1%
	(severe)	0.4%

Gastrointestinal Disorders

Nausea / Vomiting / Diarrhea	2.3%
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Adverse reactions having an incidence of <1%:

Cardic Disorders: Tachycardia (0.3%); bradycardia* (0.1%); extrasystoles (0.1%); left bundle branch heart block (0.1%); anginal symptoms (0.1%); arrhythmia* (0.1%).

Eye Disorders: Blurred vision (0.1%); sensation of pressure in eyes (0.1%).

Immune System Disorders: Urticaria (0.8%); respiratory symptoms (0.3%); angioedema and lip swelling (0.1%); Quincke's edema (0.1%).

Nervous System Disorders: dysgeusia (0.4%); restlessness/anxiety (0.3%); headache (0.3%); paresthesia (0.2%): arm or face; hypoesthesia (0.1%); dizziness (0.1%); vertigo (0.1%); vegetative dystonia (0.1%).

Respiratory, Thoracic and Mediastinal Disorders: Respiratory symptoms (0.3%); sneezing, cough, bronchospasm*; sore throat (0.1%).

Vascular Disorders: hypotension* (0.4%); collapse/loss of consciousness (0.3%); hypertension (0.1%).

Other Reactions: knee swelling/pain (0.1%); shoulder pain (0.1%); venous pressure (0.1%); numbness (0.1%); shivers (0.1%); popliteal region tension (0.1%); septicemia (0.1%).

Postmarket Adverse Drug Reactions

Adverse drug reactions reported subsequent to market introduction in Canada are presented below and are also grouped by the following denotations:

^a may be associated with injection site reaction

^b associated with intravascular use only

* life-threatening and/or fatal cases have been reported

† Endocrine Disorders - Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast

media administration to adult and pediatric patients, including infants. Some patients were treated for hypothyroidism

Cardiac disorders:	cardiac arrest*, cardiac rhythm or function disturbances, chest pain / discomfort, cyanosis*, cardiac failure*, myocardial ischemia* / infarction*, palpitations
Ear and labyrinth disorders:	hearing disorders, hearing disturbances
Endocrine disorders: †	thyroid disorder, thyrotoxic crisis
Eye disorders:	conjunctivitis, blurred / disturbed vision, lacrimation, photophobia, vision disturbances
Gastrointestinal disorders:	abdominal pain, dysphagia, swelling of the salivary glands, throat irritation
General disorders and administration site conditions:	chills, edema ^a , inflammation and soft tissue injury in case of extravasation ^a , malaise, pallor, warmth ^a
Immune system disorders:	anaphylactic reactions*, anaphylactoid reactions* / hypersensitivity*, anaphylactoid shock*
Investigations:	body temperature increased
Musculoskeletal, connective tissue and bone disorders:	hypertonia, compartment syndrome in case of extravasation ^b
Nervous system disorders:	amnesia, cerebral ischemia / infarction*, coma*, convulsion*, hypoesthesia, paresis / paralysis, somnolence, speech disorders, speech disturbances, stroke*, transient cortical blindness ^b , tremor, brain edema ^{*b} , vasovagal reactions, agitation, confusional state
Renal and urinary:	renal failure ^b , renal impairment
Respiratory, thoracic and Mediastinal disorders:	asthma*, dyspnea*, hoarseness, laryngeal*/pharyngeal*/tongue/face edema, laryngeal/pharyngeal spasm, mucosal swelling, pulmonary edema*, respiratory insufficiency*, respiratory arrest*, respiratory distress, rhinitis, transient disturbances in respiratory rate, aspiration*

Skin and subcutaneous tissue disorders: erythema, bullous conditions (eg, Stevens-Johnson's or Lyell syndrome), hyperhidrosis, pruritus, rash

Vascular disorders: blood pressure disturbances, shock^a, thromboembolic events^b, thrombophlebitis, vasculitis (severe), vasodilatation, vasospasm^b, venous thrombosis

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

The majority of the reactions after myelography or use in body cavities occur some hours after the administration.

ULTRAVIST is not indicated for use intrathecally or for use in endoscopic retrograde cholangiopancreatography (ERCP) (see **INDICATIONS AND CLINICAL USE**).

The following ADRs have been reported for ULTRAVIST with intrathecal use:

Nervous system disorders: chemical meningitis and meningism

Based on experience with other nonionic contrast media, the following adverse drug reactions may occur if ULTRAVIST is administered intrathecally:

General disorders and Administration site conditions: back pain, injection site pain, micturition disorder, pain in extremities

Nervous system disorders: aseptic meningitis, EEG abnormal, neuralgia, paraplegia

Psychiatric disorders: psychosis

In addition to the adverse drug reactions listed above, the following have been reported when ULTRAVIST is used for ERCP:

Endocrine: elevation of pancreatic enzyme levels, pancreatitis

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Center.

Intravascular Overdose:

Symptoms may include fluid and electrolyte imbalance, renal failure, cardiovascular and pulmonary complications. An overdose of ULTRAVIST (iopromide) should be treated by support of vital functions and prompt institution of symptomatic therapy.

ULTRAVIST is dialyzable. In the event of accidental intravascular overdose, water and electrolyte losses must be compensated by infusion.

DOSAGE AND ADMINISTRATION

General Information

Solutions of ULTRAVIST (iopromide), like those of other radiopaque contrast agents, should be at or close to body temperature when injected. As with other sterile parenteral products, ULTRAVIST should not be withdrawn from the vial except immediately prior to use (see **WARNINGS**). ULTRAVIST should not be mixed with other medicinal products to avoid the risk of possible incompatibilities. Any unused portion should be discarded.

For additional instructions see **Stability and Storage Recommendations**.

Vials containing contrast medium solutions are not intended for the withdrawal of multiple doses, with the exception of ULTRAVIST Pharmacy Bulk Vials (see **AVAILABILITY OF DOSAGE FORMS**, and **DOSAGE AND ADMINISTRATION, DIRECTIONS FOR MULTIPLE DISPENSING FROM PHARMACY BULK VIALS**). The rubber stopper should never be pierced more than once. The use of a cannula or needle with a long tip and a maximum diameter of 18 G is recommended for piercing the stopper and drawing up the contrast medium. With the exception of ULTRAVIST Pharmacy Bulk Vials (see **DOSAGE AND ADMINISTRATION, DIRECTIONS FOR MULTIPLE DISPENSING FROM PHARMACY BULK VIALS**), any contrast solution not used in one examination for a given patient is to be discarded.

In the case of abdominal angiography and urography, the diagnostic yield is increased if the bowels are empty of fecal matter and gas. It may be necessary to administer an enema or laxative in the evening prior to examination, provided purging of the bowels is not contraindicated.

In infants and young children, prolonged fasting, restriction of fluids and the administration of a laxative before the examination are contraindicated.

DIRECTIONS FOR MULTIPLE DISPENSING FROM PHARMACY BULK VIALS

The transferring of ULTRAVIST from Pharmacy Bulk Vials should be performed in a suitable work area, utilizing an aseptic technique. The container closure may be penetrated only one time, utilizing a suitable transfer device.

Once punctured, the withdrawal of container contents should be accomplished without delay. Any unused portion must be discarded.

Multiple dispensing from Pharmacy Bulk Vials is only intended for the following presentations:

- ULTRAVIST 300: 500 mL vial
- ULTRAVIST 370: 200 mL vial and 500 mL vial

Special Populations

Newborns (< 1 month) and infants (1 month to 2 years):

Young infants (age < 1 year) and especially newborns are susceptible to electrolyte imbalance and hemodynamic alterations. Care should be taken regarding the dose of contrast medium to be given, the technical performance of the radiological procedure and the patient status.

Elderly population (aged 65 years and above):

Middle-aged and elderly patients, without significantly impaired renal function, who received ULTRAVIST 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. (see **PRECAUTIONS, Special Populations, Geriatrics**.)

Patients with hepatic impairment:

Elimination of iopromide is not affected by impaired liver function as only about 2% of the dose is eliminated via feces and iopromide is not metabolized. No dosage adjustment is considered necessary in patients with hepatic impairment.

Patients with renal impairment:

Since iopromide is excreted almost exclusively in an unchanged form via the kidneys, the elimination of iopromide is prolonged in patients with renal impairment. Biliary excretion cannot be excluded in patients with severe renal impairment. Special attention should be paid to patients with impairment of both renal and hepatic functions (see **WARNINGS**). In order to reduce the risk of additional contrast media-induced renal impairment in patients with pre-existing renal impairment, the minimum possible dose should be used in these patients. (see **PRECAUTIONS, Renal**)

In patients with impaired renal function, the plasma half-life of iopromide is prolonged according to the reduced glomerular filtration rate.

In a clinical study, the effect of renal impairment on the pharmacokinetics and safety of iopromide was evaluated in a study with 22 patients with normal or impaired renal function. The total clearance was reduced to 49.4 mL/min/1.73 m² (CV = 53%) in mildly and moderately impaired patients (CrCl: 30-80 mL/min/1.73 m², N = 10 evaluable patients) and to 18.1 mL/min/1.73 m² (CV = 30%) in severely impaired patients not dependent on dialysis (CrCl: 10-30 mL/min/1.73 m², N = 3 evaluable patients) compared to 91.3 mL/min/1.73 m² (CV = 27.3%) in the

patients with normal renal function (CrCl: >80 mL/min/1.73 m², N = 9 evaluable patients). This results in higher systemic exposure.

The mean terminal half-life is 6.1 hours (CV = 43%) in mildly and moderately impaired patients (CrCl: 30-80 mL/min/1.73 m²) and 11.6 hours (CV = 49%) in severely impaired patients not dependent on dialysis (CrCl: 10-30 mL/min/1.73 m²).

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least 30 minutes, since experience shows that the majority of all severe incidents occur within this time.

The recommended dosages of ULTRAVIST should not be exceeded. The volume of each individual injection is a more important consideration than the total dose used.

Determine the volume and concentration of ULTRAVIST 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. As with all iodinated contrast agents, lower doses may have less risk. The efficacy of ULTRAVIST below doses recommended has not been established.

EXCRETORY UROGRAPHY

Adults

Recommended doses for each concentration of ULTRAVIST:

ULTRAVIST 300: 40 - 70 mL

ULTRAVIST 370: 30 - 55 mL

The dose may be adjusted in special indications (eg, obese patients, impaired renal function), if necessary.

Children

The physiologically poor concentrating ability of the immature nephron necessitates the administration of relatively high doses of contrast medium in children.

The doses of ULTRAVIST 300 should not exceed:

Newborns (< 1 month): 4 mL/kg of body weight equivalent to 1.2 g I/kg.

Infants (1 month to 2 years): 3 mL/kg of body weight equivalent to about 1.0 g I/kg.

Children (2 to 11 years): 1.5 mL/kg of body weight equivalent to about 0.5 g I/kg.

COMPUTERIZED TOMOGRAPHY (CT)

Cranial CT

The following doses are recommended and should not be exceeded:

ULTRAVIST 300: 70 - 140 mL

ULTRAVIST 370: 70 - 105 mL

Whole-body CT

In whole-body computerized tomography, the necessary doses of ULTRAVIST and the rates of administration depend on the organs under investigation, the diagnostic problem and, in particular, the different scan and image reconstruction times of the scanner.

Recommended doses for each concentration of ULTRAVIST:

ULTRAVIST 300: 100 - 150 mL

ULTRAVIST 370: 80 - 120 mL

ANGIOGRAPHY

The dosage of ULTRAVIST depends on the age, weight, cardiac output and general condition of the patient, the clinical problem, examination technique, and the nature and volume of the vascular region to be investigated. The following dosages may serve as a guide:

PROCEDURE	ULTRAVIST CONCENTRATION (mg I/mL)	USUAL RECOMMENDED SINGLE DOSE (mL/injection)
Cerebral Arteriography:		
Aortic arch angiography	300	40 - 80
Retrograde carotid angiography	300	30 - 40
Common carotid	300	6 - 12
Internal carotid	300	5 - 12

External carotid	300	4 - 8
Vertebral artery	300	6 - 10

Aortography:

Thoracic aortography	300	50 - 80
Abdominal aortography	300	40 - 60

Peripheral angiography:

Selective arteriography	300	8 - 12
Aorto-femoral runoffs	300	40 - 80

Phlebography:	300	60 - 90
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Angiocardiography:

Left ventriculography	370	30 - 60
Coronary arteriography	370	5 - 8

Pediatric Angiography

ULTRAVIST 370 mg I/mL is indicated for pediatric angiocardiography. Pediatric dosing is suggested proportional to body weight, and based on cardiac output and general condition of the patient, the clinical problem, examination technique, and the nature and volume of the vascular region to be investigated.

ARTHROGRAPHY

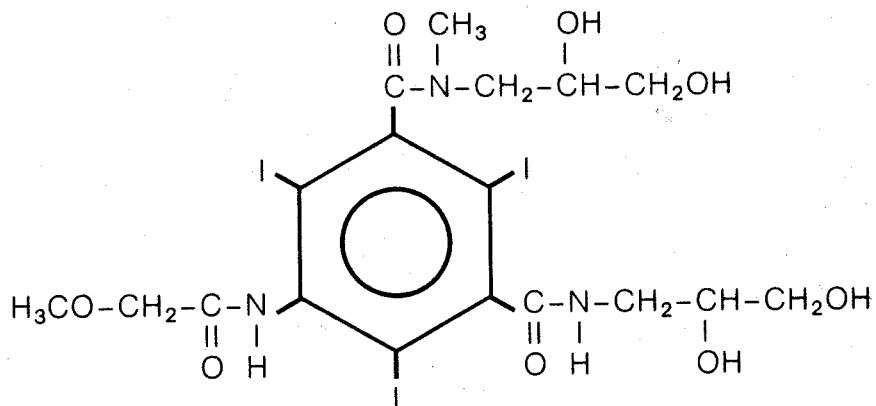
Intraarticular injections of contrast media should be monitored by fluoroscopy to ensure adequate injection technique and opacification while preventing over distention of the joint space. Excessive dilution of the contrast medium should be avoided.

PROCEDURE	ULTRAVIST CONCENTRATION (mg I/mL)	USUAL RECOMMENDED SINGLE DOSE (mL/injection)
Knee	300	5 - 11
	370	5 - 11

PHARMACEUTICAL INFORMATION

Drug Substance

Structural Formula:



Molecular Formula: $\text{C}_{18}\text{H}_{24}\text{I}_3\text{N}_3\text{O}_8$

Molecular Weight: 791.12

Chemical Name: 5-methoxyacetylamino-2,4,6-triiodoisophthalic acid[(2,3-dihydroxy-N-methylpropyl)-(2,3-dihydroxypropyl)] diamide

Non-medicinal Ingredients: calcium disodium edetate (EDTA), hydrochloric acid and tromethamine. Preservative-free. pH has been adjusted to between 6.5 and 8.0 with hydrochloric acid.

Physical Properties:

	ULTRAVIST 300	ULTRAVIST 370
Iodine concentration (mg/mL)	300	370
Iopromide concentration (mg/mL)	623.0	769.0
Viscosity (mPa•s or cp) at 20°C	8.7	20.1
at 37°C	4.6	9.5
Osmotic pressure at 37°C (MPa)	1.59	2.02
(atm)	15.7	19.9
Osmolality at 37°C (osm/kg H ₂ O)	0.61	0.77
Specific gravity at 37°C	1.33	1.409

Stability and Storage Recommendations

ULTRAVIST (iopromide) should be stored between 15°C and 30°C and protected from light.

ULTRAVIST should be visually inspected and used only if:

- it is clear and within the normal colorless to pale yellow range
- it contains no particulate matter (including crystals)
- the container does not appear to be defective

Since ULTRAVIST is a highly concentrated solution, crystallization (milky-cloudy appearance and/or sediment at bottom, or floating crystals) may occur very rarely.

Discard unused portions.

AVAILABILITY OF DOSAGE FORMS

ULTRAVIST (iopromide) is a sterile colorless to pale yellow solution of iopromide in water and contains no preservative. Solutions do contain tromethamine (0.24%) as a buffer and calcium disodium edetate (EDTA) 0.1 mg/mL as a sequestering agent. The pH has been adjusted to between 6.5 and 8.0 with hydrochloric acid.

ULTRAVIST 300 (iopromide 62.3%) provides 623 mg of iopromide per mL equivalent to 300 mg of organically bound iodine per mL. It is supplied in 50, 100, and 150 mL vials. Pharmacy Bulk Vials are supplied in 500 mL vials.

ULTRAVIST 370 (iopromide 76.9%) provides 769 mg of iopromide per mL equivalent to 370 mg of organically bound iodine per mL. It is supplied in 50, and 100 mL vials. Pharmacy Bulk Vials are supplied in 200 mL and 500 mL vials.^a

^a (Not all presentations may be available in Canada.)

PHARMACOLOGY

PHARMACODYNAMICS

Hemodynamics

In isolated perfused rabbit hearts, iopromide (370 : 1480 mg I) produced initial vasodilatation with increased coronary flow and a positive inotropic effect; ventricular fibrillation subsequently complicated these observations.

Anesthetized rats given a single intravenous administration of iopromide (1110 mg I/kg) showed increases in mean arterial pressure, maximum rate of increase in left ventricular pressure (dp/dt), cardiac minute volume, end diastolic pressure and myocardial oxygen consumption during the first 2 to 3 minutes post injection. Heart rate was transiently lowered immediately post injection and vascular resistance was reduced significantly. Extrasystoles occurred during the first 56 seconds post injection.

Cardiovascular effects in anesthetized cats given a single intravenous injection of iopromide 1110 mg I/kg included increases in blood pressure, end diastolic pressure, central venous pressure, pulmonary artery pressure, cardiac minute volume, and contractility; peripheral resistance was decreased and heart rate was lowered transiently.

Dogs injected with iopromide (3 g I) into the coronary arteries following cardiac catheterization demonstrated a positive inotropic effect and slightly decreased coronary sinus blood flow.

Lungs

Tests of lung and cardiovascular function in the guinea pig after intravenous iopromide administration (1-2 g I/kg) revealed an increased negativity of the expiratory intrapleural pressure, increased respiratory rate, decreased blood pressure, decreased compliance and increased airways resistance.

Arterial Tolerance

The ED₅₀ of iopromide for femoral artery pain in the rat was greater than 3.0 g I/kg.

The rat showed only slight behavioural anomalies after up to 3 g I/kg were administered by the carotid artery; little pain response was seen with femoral artery administration of up to 4 g I/kg. Iopromide concentrations greater than 320 mg I/mL were less painful than iohexol or iopamidol in the femoral artery.

Central Nervous System

Intracerebral administration of iopromide in the rat revealed an ED₅₀ of 86 mg I/kg and an LD₅₀ of 588 mg I/kg. Intracisternal administration in the rat resulted in an ED₅₀ of 53 mg I/kg and an LD₅₀ of 222 mg I/kg.

Intraarterial administration into the common carotid artery of the rat resulted in an ED₅₀ of 2.3 g I/kg. Iopromide was better tolerated than iopamidol and meglumine ioglicinate.

Vertebral angiography in the rabbit was associated with greater brachycardia after iopromide administration (3.5 g I/animal) than after iopamidol or metrizamide at equivalent doses.

Renal

Radiography of the renal parenchyma in the dog following a single intravenous administration of iopromide 300 to 600 mg I/kg provided good to moderate visualization of the renal parenchyma. Plasma iodine concentrations after 300 mg I/kg i.v. were 2.6 to 3.0 mg I/m and decreased to 0.8 to 0.9 mg I/mL 20 minutes postadministration. After 600 mg I/kg i.v. plasma iodine concentrations were 5.2 to 6.2 mg I/mL and dropped to 1.5 - 2.0 mg I/mL within 20 minutes post administration. A decrease in hematocrit was also observed.

After renal arteriography in the rat, greater albuminuria was noted after administration of iopromide (400 mg I/kg) than in the controls; however, no statistically significant differences were noted between iopromide, iohexol and iopamidol in this respect.

In rabbits, the potential of iopromide to cause renal damage was determined after a single intravenous administration of 1 to 10.5 g I/kg. Findings included increased protein excretion, increased GGT, increased serum urea-N, increased serum creatinine and changes in SGOT, SGPT, and alkaline phosphatase levels. Kidney changes (tubular necrosis, pallor, dilated tubules) and increased kidney weight were also apparent. In white rabbits a single intravenous dose of iopromide (5 g I/kg) had a greater effect than iopamidol on serum creatinine, serum urea-N, urine protein and flow as well as on the occurrence of histological findings.

An investigation of renal function in rhesus monkeys after a single intravenous injection of iopromide (5 g I/kg) revealed no abnormalities.

Other

In vitro and in vivo investigations with iopromide revealed very little plasma protein binding (0.9%) and demonstrated only a slight influence on erythrocyte morphology in comparison with iosimide, metrizamide and ioglicinate. A low rate of lysozyme inhibition ($ID_{50}=142$ mg l/mL), hemolysis inhibition ($ID_{50}=15.2$ mg l/mL) and complement activation ($ED_{50}=176$ mg l/mL) similar to that of other nonionic contrast media was also determined.

In one investigation, to determine histamine release from rat mast cells, contamination of the test substance (150 mg l/mL) caused an extremely high histamine release (82%); this investigation was non-reproducible. Histamine release in another investigation with rat mast cells was much lower (7%) and compared favorably with metrizamide and iopamidol.

PHARMACOKINETICS

Following a single intravenous injection of ^{125}I -iopromide 1 and 10 g l/kg in rats, 56% and 26% of the dose, respectively, was excreted in the urine within 30 minutes. Ninety per cent of either dose was excreted in the urine, and 10% in the stool, by the seventh day after administration. The pre-injection isomeric ratio was unchanged and no metabolites were observed in urine or bile. Accumulation of iodine in the thyroid gland was noted in the rat after the radio-labelled drug was administered. In another experiment, the disappearance of 3H -iopromide from the thyroid was similar to that for other organs, indicating that the accumulation of iodine in the thyroid was not due to an

accumulation of iopromide. The plasma half-life in the conscious rat was short at about 15 minutes.

In the dog the plasma half-life was 45 minutes and total plasma clearance was about 3 mL/min/kg, indicating primary elimination by glomerular filtration in the kidney. The apparent volume of distribution of iopromide corresponded to the extracellular compartment. No metabolites were apparent. The ratio of stereoisomers for the drug was unchanged in the urine.

In the rat ^{125}I -iopromide appeared not to cross the placental barrier appreciably, although in rabbits, radioactivity which approximated 5-10% of the maternal plasma level was measured in the fetus.

TOXICOLOGY

Acute Toxicity

Iopromide, by single intracisternal injection, was less well tolerated in the rat than was metrizamide. The LD_{50} for iopromide was 222 mg I/kg and for metrizamide it was 325 mg I/kg ($P \leq 0.05$). Toxic effects included various motor disturbances seen in all animals with survivors recovering within 48 hours.

In two studies in rats, the LD_{50} of iopromide was found to be 14.5 g I/kg and > 14.8 g I/kg, following a single intravenous injection. In weanling rats the LD_{50} of iopromide was 15.5 g I/kg following a single intravenous injection. Signs of toxicity included apathy, prone posture, spastic gait, ruffled fur and necrosis/discoloration at the

injection site. Surviving rats were free of neurologic symptoms within 48 hours. Rats which died showed renal pallor, pulmonary edema and hydrothorax.

The intravenous LD₅₀ of iopromide in mice was greater than 18.5 g I/kg. Signs of toxicity were similar to those seen in the rat. Additionally, paleness of the liver occurred in mice that died.

The LD₅₀ following a single injection into the right carotid artery of rats was about 50% of the intravenous LD₅₀. Seizures occurred in all animals after 10.0 g I/kg.

Injections of iopromide, metrizamide or iopamidol (3.5 g I/animal) into the vertebral artery of rabbits were equally well tolerated with little evidence of arterial (intracranial) spasm following any of these agents.

In the beagle dog the intravenous LD₅₀ was greater than 10 g I/kg. Toxic effects included apathy, diuresis, blood-stained feces, cutaneous erythema, auricular vesiculation and swollen lips and eyelids. However, no dogs died and no abnormalities were seen at autopsy.

Subacute Toxicity

Iopromide was administered to rats and beagle dogs of both sexes for 4-5 weeks. No animals died and no severe adverse effects were recorded. Mild to moderate vacuolization of the hepatocytes in rats, and slight to moderate vacuolization of the proximal tubular epithelial cells in dogs were observed after 3.7 g I/kg

Local Tolerance

Local tolerance studies in rabbits after a single intravenous or intraarterial application into the ear vessels did not give any evidence for unequivocal local changes at the administration site.

After a single intramuscular injection, the same animal species showed slight local reactions, which were only slightly more marked than those observed after 0.9% (w/v) NaCl solution.

Reproduction and Teratology

Pregnant female rats, after daily intravenous administration (days 6 to 15 of gestation) with doses of 0.37, 1.11, and 3.7 g l/kg/day showed adverse local reactions from 1.11 g l/kg/day and a slight decline in body weight gain after 3.7 g l/kg/day. Fetal examinations revealed an increased incidence of minor skeletal anomalies at all doses and additional 14th ribs in the high dose group.

A similar investigation in the rabbit was invalid owing to an unacceptably high content of free amines in the test substance. Findings in the doe included convulsions and increased mortality. In the fetus findings included slight retardational effects in surviving animals, increased embryomortality, increased frequency of supernumerary 13th ribs and increased incidence of postural limb anomalies.

Female rabbits received doses of 0.37, 1.11, and 3.7 g l/kg/day on days 6-18 of gestation. Fetal observations included increased minor external anomalies, increased rate of retarded ossification of sternebrae at 1.11 g l/kg/day and above, as well as,

decreased mean fetal weight and increased rate of minor visceral anomalies or variations at the highest dose. There was an increased mortality rate in does after 3.7 g l/kg/day.

Rabbits, administered dosages of 0.4, 1.2, 3.6 g l/kg/day, during days 6 to 18 of gestation, showed no change in general condition, mortality rate, or incidence of abortions. No effect was observed on the number, size, weight and sex of the fetuses or on pre-and postimplantational loss or incidence of fetal anomalies. Determination of gamma-glutamyl transferase in 24 h urine, urea nitrogen, and serum creatinine revealed no compound-related effects. There was no change in the kidney in respect to absolute or relative organ weight, or histology.

Mutagenicity

No positive mutagenic responses were observed for iopromide in the mouse during the micronucleus and dominant lethal tests. No evidence of mutagenicity was observed in the Ames test with *Salmonella typhimurium*. Similarly, there was no indication of clastogenic potential in the human lymphocyte test.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

ULTRAVIST®

iopromide injection

ULTRAVIST® 300

(iopromide injection 62% w/v, 300mg l/ml)

ULTRAVIST® 370

(iopromide injection 77% w/v, 370mg l/ml)

For Professional Use Only

Read this carefully before you start taking **ULTRAVIST** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ULTRAVIST**.

What is ULTRAVIST used for?

- ULTRAVIST is a contrast medium for radiographic (X-ray) or computed tomography (CT) examinations.
- ULTRAVIST is for diagnostic use only.

How does ULTRAVIST work?

ULTRAVIST contains iodine. X-rays are unable to pass through contrast media because they are absorbed by the iodine. The areas of your body where ULTRAVIST is distributed after it is injected into your bloodstream, or joint, or a body cavity, become visible during the X-ray or CT examination. Depending on the mode of administration and the administered strength, ULTRAVIST provides visualization of the veins and arteries, detection of abnormalities in the urinary system, kidney, brain, spine, heart, joints and body cavities.

What are the ingredients in ULTRAVIST?

Medicinal ingredients: iopromide

Non-medicinal ingredients: calcium disodium edetate (EDTA), hydrochloric acid and tromethamine.

ULTRAVIST comes in the following dosage forms:

ULTRAVIST is an aqueous solution for injection into a vein or body cavity. It is supplied in two strengths. ULTRAVIST 300 provides 623 mg of iopromide per mL (equal to 300 mg of organically bound iodine per mL). ULTRAVIST 370 provides 769 mg of iopromide per mL (equal to 370 mg of organically bound iodine per mL).

ULTRAVIST is packaged in vials.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ULTRAVIST. Talk about any health conditions or problems you may have, including if you:

- You have had a previous reaction to contrast media
- You suffer or have suffered from an allergy (eg, seafood allergy, hay fever, hives) or bronchial asthma

- You are allergic (hypersensitive) to iopromide or to any of the other ingredients of ULTRAVIST
- Your kidneys do not work properly
- You have disturbances of both kidney and liver function
- You are taking medicine that affects your kidney function
- You have had a kidney transplant
- You suffer from dehydration
- You have diabetes
- You have heart disease or circulatory disease
- You suffer from a vascular condition in which you have clotting of some small blood vessels in the hands or feet (Buerger's disease or thromboangiitis obliterans)
- You have high blood pressure (hypertension)
- You have a special kind of high blood pressure caused by a rare tumour of the adrenal gland which sits near the kidney (pheochromocytoma)
- You have, or you are suspected to have a thyroid gland that is overactive, or you have a thyroid nodule, or you have a swelling of the neck caused by enlargement of the thyroid gland (bland nodular goiter)
- You have a circulatory problem in the brain (for example, cerebral arteriosclerosis or cerebral artery spasm)
- You suffer from brain conditions with seizures or from other diseases of the nervous system
- You suffer from a condition where you have increased intracranial pressure or a disrupted blood-brain barrier
- You suffer from cancer of the blood cells (multiple myeloma)
- You suffer from an overproduction of special proteins (paraproteinemia)
- You suffer from a harmful accumulation of homocysteine in the body (homocystinuria)
- You have sickle cell disease
- You have a breathing condition where too much air collects deep in the lungs (pulmonary emphysema)
- You suffer from a condition in which the muscles become weak and tire easily (myasthenia gravis)
- You are pregnant or think you might be pregnant (even if you are not sure)
- You are breast-feeding or intend to breast-feed, since breast-feeding should be stopped for 48 hours following ULTRAVIST administration
- You are planning to have a special procedure to allow your doctor to visualize your gallbladder (oral cholecystography)
- Before you receive ULTRAVIST, your doctor will screen you for the function of your kidneys in order to decide whether the intended examination is possible or not.

Other warnings you should know about:

Thyroid Function

Contrast media containing iodine, such as ULTRAVIST, may change thyroid activity in some patients, both in adults and infants. This may cause:

- hypothyroidism (i.e. too little thyroid hormones in the blood)

or

- hyperthyroidism (i.e. too much thyroid hormones in the blood)

Thyroid Function in infants

Contrast media containing iodine may cause hypothyroidism in infants, especially infants born too soon that:

- can continue for several weeks to a month after treatment
- can harm growth and development
- can harm mental growth
- may require treatment
- can cause symptoms such as:
 - fatigue, shortness of breath, low heart rate
 - reduced appetite, feeling cold, weight gain
 - muscle stiffness

Contact your doctor if these symptoms happen to your infant.

Your doctor may order blood tests for your infant after treatment to follow thyroid hormone levels in the blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ULTRAVIST:

- beta-blockers (medicines used to treat high blood pressure or other heart conditions)
- biguanides (eg, metformin - a medicine used to treat diabetes)
- interleukin
- radioactive substances for the thyroid gland
- Your doctor will advise you how to take these medicines before the examination.
- Some medical tests (eg, thyroid function tests, blood tests for clotting [coagulation] or blood clot breakdown [fibrinolysis] or tests for complement proteins [involved in immunity and inflammation]) may be affected by the use of ULTRAVIST. Tell your doctor if you have any of these tests scheduled.

How to take ULTRAVIST:

ULTRAVIST will be given to you by a healthcare professional who is experienced in the use of radiopharmaceuticals.

Usual dose:

- Your doctor will make sure that you receive enough fluid before your examination.
- You may be given an enema or laxative on the evening before your CT or X-ray examination.
- The actual dose (volume) of ULTRAVIST that is right for you will be worked out by your health professional and will depend on your age, body weight and the type of examination that is being done. The speed at which ULTRAVIST is injected, and the length of time until the X-rays or CT are taken will also depend of the type of X-ray or CT being done.

Overdose:

If you think you have taken too much ULTRAVIST, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Overdosing is unlikely. If it does happen, your doctor will treat any symptoms that follow.

What are possible side effects from using ULTRAVIST?

These are not all the possible side effects you may feel when taking ULTRAVIST. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, ULTRAVIST can cause side effects, although not everybody gets them.

The most common side effect of ULTRAVIST is having a sensation of warmth.

Common side effects observed in clinical trials (between 1 and 10 in every 100 patients are likely to get these):

- sensation of warmth (severe)
- sensation of pain (slight to moderate)
- feeling sick (nausea), vomiting, diarrhea

Uncommon side effects observed in clinical trials (between 1 and 10 in every 1 000 patients are likely to get these):

- severe sensation of pain
- restlessness/anxiety
- pins and needles of the arm or face (paresthesia)
- sensation of whirling/dizziness (vertigo)
- taste sensation (dysgeusia)
- headache
- shoulder pain
- numbness
- sore throat

Side effects reported from postmarketing experience:

- palpitations,
- hearing disorders, hearing disturbances
- discomfort in bright light (photophobia), pressure over the eyes
- stomach (abdominal) pain
- swelling of salivary glands, throat irritation
- change in body temperature. chills, shivers, sweating
- feeling unwell (malaise)
- paleness (pallor)
- tight muscles (hypertonia)
- decreased sensation (hypoesthesia)
- tremor
- agitation
- runny nose (rhinitis)

Serious side effects and what to do about them		
Symptom/ Effect	Talk to your healthcare professional	
	Only if severe	In all cases
UNCOMMON		
Collapse (including vasovagal reactions)		✓
Low blood pressure (hypotension), high blood pressure (hypertension)	✓	
Serious allergy-like (anaphylactoid) reactions, sometimes fatal, with symptoms such as shock, swelling of the throat, face, tongue, lips (laryngeal/pharyngeal/tongue/face edema, angioedema, Quincke's edema, Laryngeal spasm, mucosal swelling), difficulty swallowing (dysphagia), difficulty in breathing (respiratory symptoms, bronchospasm, dyspnea, asthma), hives (urticaria), coughing, sneezing, redness of the eyes (conjunctivitis). Blurred/disturbed vision, tearing (lacrimation)		✓
Swelling or pain around the knee	✓	
SIDE EFFECTS FROM POSTMARKETING EXPERIENCE		
Blood clots (thromboembolic events, venous thrombosis)		✓
Blood vessel inflammation (thrombophlebitis, vasculitis (severe))		✓
Chest pain/ discomfort (myocardial ischemia/ infarction)		✓
Heart stopped (cardiac arrest)		✓
Inflammation and tissue injury at injection site, in case of extravasation	✓	
Lips turning blue (cyanosis)		✓
Memory loss (amnesia)		✓
Paresis/paralysis		✓
Possible heart rhythm disturbance (rapid or slow heart beat)	✓	
Redness of the skin (erythema and/or vasodilation), itching (pruritus), rash	✓	
Seizure (convulsion)		✓
Stevens Johnson's or Lyell syndrome with symptoms such as redness, pain swelling or blistering of the skin		✓
Stroke, with symptoms including but not limited to sudden onset headache and/or weakness, difficulty speaking, blurred vision, sleepiness (somnolence), confusion		✓
Temporary loss of vision (transient cortical blindness)		✓

Serious side effects and what to do about them		
Taking foreign material into lungs (aspiration)	✓	
Pressure in muscle and related tissue with symptoms such as pain, hardness, swelling, and “pins and needles” feeling, related to the condition known as compartment syndrome where a significant volume of the contrast agent has escaped into the tissues, and can be life-threatening		✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

ULTRAVIST should be stored between 15°C and 30°C and protected from light.

If you want more information about ULTRAVIST:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer’s website <http://www.bayer.ca> or by calling Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

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