NEW ZEALAND DATA SHEET

ULTRAVIST® (iopromide)

1. NAME OF THE MEDICINE

Iopromide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultravist 240 solution for injection / infusion contains 499 mg of iopromide per mL, equivalent to 240 mg iodine
Ultravist 300 solution for injection/infusion contains 623 mg of iopromide per mL, equivalent to 300 mg iodine
Ultravist 370 solution for injection/infusion contains 769 mg of iopromide per mL, equivalent to 370mg iodine

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

ULTRAVIST solution for injection/infusion is a clear, colourless to pale yellow solution, free of particles and has a pH of 6.5 - 8.0. It contains no antimicrobial preservatives.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

This medicine is for diagnostic use only.

For intravascular use and use in body cavities.

Contrast enhancement in computerised tomography (CT), arteriography and venography, intravenous/intra-arterial digital subtraction angiography (DSA), intravenous urography, use for ERCP, arthrography and examination of other body cavities.

ULTRAVIST 240: Also for intrathecal use.
ULTRAVIST 370: Especially for angiocardiography.
ULTRAVIST 300 / 370: Not for intrathecal use.

4.2 DOSE AND METHOD OF ADMINISTRATION

Administration Technique

Visual inspection prior to use

Contrast media should be visually inspected prior to use and must not be used in the presence of particulate matter (including crystals), if discoloured, or if the container is defective in any way. As ULTRAVIST is a highly concentrated solution, crystallisation (evident as a milky-cloudy appearance and/or sediment or floating crystals) may occur very rarely.

Warming prior to use

Contrast media that are warmed to body temperature before administration are better tolerated and can be injected more easily because of reduced viscosity.

ULTRAVIST must not be mixed with any other medicines, such as agents for the prophylactic treatment of hypersensitivity reactions, to avoid the risk of possible incompatibilities.

Avoid rapid dispersion of the medium.

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

Administration of contrast media should be performed by qualified personnel with the appropriate procedures and equipment.

Sterile technique must be used in all injections involving contrast media. ULTRAVIST does not contain preservatives.

The patient must attend for examination fasting but adequately hydrated. Disorders of the water and electrolyte balance must be corrected. This applies in particularly to patients who are predisposed to such disturbances.

Single Dose Vials and Bottles

The contrast medium solution should not be drawn into the syringe, or the infusion bottle attached to the infusion set until immediately before the examination.

The rubber stopper should never be pierced more than once to prevent large amounts of microparticles from the stopper getting into the solution. The use of cannulas with a long tip and a maximum diameter of 18 G is recommended for piercing the stopper and drawing up the contrast medium (dedicated withdrawal cannulas with a lateral aperture e.g. Nocore - Admix cannulas, are particularly suitable).

Any contrast solution not used in one examination for a given patient must be discarded. ULTRAVIST does not contain preservatives.

Unused ULTRAVIST in opened containers must be discarded ten hours after first opening the container.

Dosage for intravascular use

Dosage should be adapted to age, weight, clinical question and examination technique.
The dosages given below are recommendations only and represent common doses for an average normal adult weighing 70 kg. Doses are given for single injections or per kilogram (kg) body weight (BW) as indicated below.

Generally, doses of up to 1.5 g iodine per kg body weight are well tolerated.
After administration, the patient should be observed for at least 30 minutes, since the majority of reactions occur within this time.

Intravenous urography

The following dosages are recommended.

Adults

Increasing the dose in adults is possible if this is considered necessary in special indications.

Adolescents and Adults	0.3 g I/kg body weight	1.3 mL/kg BW ULTRAVIST 240 1.0 mL/kg BW ULTRAVIST 300 0.8 mL/kg BW ULTRAVIST 370

Children
The physiologically poor concentrating ability of the still immature nephron of infantile kidneys demands relatively high doses of contrast medium.

Newborns (< 1 month)	1.2 g I/kg body weight	5.0 mL/kg BW ULTRAVIST 240 4.0 mL/kg BW ULTRAVIST 300 3.2 mL/kg BW ULTRAVIST 370
Infants (1 month - 2 years)	1.0 g I/kg body weight	4.2 mL/kg BW ULTRAVIST 240 3.0 mL/kg BW ULTRAVIST 300 2.7 mL/kg BW ULTRAVIST 370
Children (2 - 11 years)	0.5 g I/kg body weight	2.1 mL/kg BW ULTRAVIST 240 1.5 mL/kg BW ULTRAVIST 300 1.4 mL/kg BW ULTRAVIST 370

Filming Times
When the above dosage guidelines are observed and ULTRAVIST 300/370 is injected over 1 to 2 minutes (3 - 5 minutes in the case of ULTRAVIST 240), the renal parenchyma is usually highly opacified 3 to 5 minutes (5 - 10 minutes for ULTRAVIST 240) and the renal pelvis with the urinary tract 8 to 15 minutes (12 - 20 minutes for ULTRAVIST 240) after the start of administration. The earlier time should be chosen for younger patients and the later time for older patients.

Normally, it is advisable to take the first film as early as 2 - 3 minutes after administration of the contrast medium. In newborns, infants and patients with impaired renal function later films may improve visualisation of the urinary tract.

Insufficient contrast necessitates late films.

Computerised tomography (CT)

Whenever possible, ULTRAVIST should be injected as an i.v. bolus, preferably using a power injector. Only for slow scanners about half of the total dosage should be administered as a bolus and the rest within 2 - 6 minutes to guarantee a relatively constant - though not maximum - blood level.

Spiral CT in single and especially in multi-slice technique allows the rapid acquisition of a volume of data during a single breath-hold. To optimise the effect of the i.v. administered bolus (80 - 150 mL ULTRAVIST 300) in the region of interest (peak, time and duration enhancement), the use of an automatic power injector and bolus tracking is strongly recommended.

Whole-Body CT

ULTRAVIST 300: 0.5 – 1.5 mL/kg body weight

In whole-body computerised tomography, the necessary doses of contrast medium 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 scanners in use.

Cranial CT

The following adult dosages are recommended for cranial CT:
ULTRAVIST 240: 1.5 - 2.5 mL/kg body weight
ULTRAVIST 300: 1.0 - 2.0 mL/kg body weight
ULTRAVIST 370: 1.0 - 1.5 mL/kg body weight

Paediatric Contrast Enhanced CT (CECT, head and body)

ULTRAVIST 300 mg I/mL is indicated for intravenous administration for CECT of the head and body. Paediatric dosing is suggested proportional to body weight. The suggested dose is 1 - 2 mL/kg. Total dose for the procedure should not usually exceed 3 mL/kg.

Conventional Angiography

The dosage 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.

		ULTRAVIST
Cerebral angiography		
Aortic arch angiography	50 – 80 mL	300
Retrograde carotid angiography	30 – 40 mL	300
Selective angiography	6 – 15 mL	300
Thoracic aortography	50 – 80 mL	300 or 370
Abdominal aortography	40 – 60 mL	300
Angiography of the extremities		
Upper extremities		
Arteriography	8 – 12 mL	300
Venography	50 – 60 mL	240
	15 – 30 mL	300
Lower extremities		
Arteriography	20 – 30 mL	300
Venography	50 – 80 mL	240
	30 – 60 mL	300
Angiocardiography		
Selective, in the individual cardiac cavities:	40 – 60 mL	370
Coronarangiography	5 – 8 mL	370

Paediatric Angiocardiography

ULTRAVIST 370 is indicated for intra-arterial and intra-cardiac administration in the radiographic contrast evaluation of the heart cavities and of the major arteries. Paediatric dosing is suggested proportional to body weight. The suggested dose is 1 - 3 mL/kg. Total dose for the procedure should not usually exceed 5 mL/kg.

Intravenous Digital Subtraction Angiography (DSA)

Adults: 30 - 60 mL ULTRAVIST 300/370

The i.v. injection of 30 – 60 mL ULTRAVIST 300 or 370 as a bolus (flow rate: 8–12 mL/second into the cubital vein; 10 - 20 mL/second into the vena cava) is only recommended for high-contrast demonstrations of the great vessels, of the pulmonary arteries and of the arteries of the neck, head, kidneys and extremities.

The period of time for which the contrast medium is in contact with the wall of the veins can be reduced by flushing with 20 to 40 mL isotonic sodium chloride solution as a bolus immediately afterwards.

Intra-arterial Digital Subtraction Angiography (DSA)

The dosages and concentrations used in conventional angiography can be reduced for intra-arterial DSA.

For high-contrast demonstration of the arteries e.g. in the regions of the head, neck and extremities, several injections of 10 - 40 mL of diluted ULTRAVIST of a strength equivalent to 150 mg iodine per mL - depending on the size of the vessels - are usually given directly or via a catheter.

Higher doses of contrast medium (about 200 mL of diluted ULTRAVIST of a strength equivalent to 150 mg iodine per mL) may be necessary in some cases to demonstrate the vessels of the lower extremity e.g. if both legs are to be examined.

General information

In the case of abdominal angiography and urography, the diagnostic yield is increased if the bowels are emptied of faecal matter and gas. On the two days prior to examination patients should, therefore, avoid flatulent food, in particular peas, beans and lentils, salads, fruit, dark and fresh bread and all kinds of uncooked vegetables. On the day before the examination patients should refrain from eating after 6 pm. It may also be appropriate to administer a laxative in the evening.

In babies and young children, however, prolonged fasting and the administration of a laxative before the examination are contraindicated.

Dosage for intrathecal use

Adults: The dosage may vary depending on the clinical problem, examination technique and the region to be investigated.

If equipment is available which shows all necessary projections to be filmed without the patient having to move and with which the instillation can be performed under fluoroscopic control, then often lower volumes are sufficient.

Please note: The more the patient moves or exerts himself after the administration of ULTRAVIST, the quicker the contrast medium will mix with the fluid of other regions of no interest. As a consequence, the contrast density decreases more quickly than usual.

After the examination the contrast medium should be directed to the lumbar region. This is achieved by placing the patient in an upright sitting position or by elevating the head of the bed by 15° for at least 6 hours. Thereafter, the patient should rest for about 18 hours to minimise any discomfort caused by leakage of cerebrospinal fluid. During this period observation for adverse reactions is advisable. Patients suspected of having a reduced seizure threshold must be kept under particularly careful observation for some hours.

Repeat Procedure: An interval of at least 48 hours should be allowed before repeat examination.

Children: The safety and effectiveness in children has not been established for intrathecal use of ULTRAVIST.

Myelography

Up to 12.5 mL ULTRAVIST 240
The maximum dose of 12.5 mL ULTRAVIST 240 corresponds to a total iodine dose of 3 g and should not be exceeded.

Please note: The more the patient moves or exerts themself after the administration, the quicker the contrast medium will mix with the fluid of other regions of no interest. As a consequence, the contrast density decreases more quickly than usual.

After the examination the contrast medium should be directed to the lumbar region. This is achieved by placing the patient in an upright sitting position or by elevating the head of the bed by 15° for at least 6 hours. Thereafter, the patient should rest for about 18 hours to minimize any discomfort caused by leakage of cerebrospinal fluid. During this period observation for adverse reactions is advisable. Patients suspected of having a reduced seizure threshold must be kept under particularly careful observation for some hours.

Repeat procedure: An interval of at least 48 hours should be allowed before repeat examination.

Dosage for use in body cavities

During arthrography, hysterosalpingography and ERCP, injections of contrast medium should be monitored by fluoroscopy.

The dosage may vary depending on the age, weight and general condition of the patient. It also depends on the clinical problem, examination technique and the region to be investigated. The dosages given below are recommendations only and represent average doses for a normal adult.

Arthrography: 5 - 15 mL ULTRAVIST 240/300/370
Hysterosalpingography: 10 - 25 mL ULTRAVIST 240
ERCP: Dosage depends generally on clinical question and size of structure to be imaged.
Other: Dosage depends generally on clinical question and size of structure to be imaged.

Dosage for 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.

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. In order to reduce the risk of additional contrast media-induced kidney injury in patients with pre-existing renal impairment, the minimum possible dose should be used in these patients (see also sections 4.4 Special Warnings and Precautions for Use, Use in renal impairment and section 5.2 Pharmacokinetic Properties).

4.3 CONTRAINDICATIONS

ULTRAVIST should not be administered to patients with known hypersensitivity or previous reaction to iodinated contrast media or any excipients in section 6.1.

Immediate repeat myelography, in the event of technical failure, is contraindicated because of overdosage considerations (see recommendation under section 4.2 Dosage and Administration).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

EVALUATE THE RISK BEFORE USE OF IOPROMIDE WHEN ANY OF THE FOLLOWING MEDICAL PROBLEMS EXIST:

For all indications

Hypersensitivity reactions

ULTRAVIST can be associated with anaphylactoid/hypersensitivity or other idiosyncratic reactions characterised by cardiovascular, respiratory and cutaneous manifestations.

Allergy-like reactions ranging from mild to severe reactions including shock are possible (see section 4.8 Adverse effects (Undesirable effects). Most of these reactions occur within 30 minutes of administration. However, delayed reactions (after hours to days) may occur.

The risk of hypersensitivity reactions is higher in case of:

- previous reaction to contrast media
- history of bronchial asthma or other allergic disorders

Particularly careful risk/benefit judgement is required in patients with known hypersensitivity to Ultravist or any excipient of Ultravist, or with a previous hypersensitivity reaction to any other iodinated contrast medium due to an increased risk for hypersensitivity reactions (including severe reactions).

However, such reactions are irregular and unpredictable in nature.

Patients who experience such reactions while taking beta blockers may be resistant to treatment effects of beta agonists.

In the event of a severe hypersensitivity reaction, patients with cardiovascular disease are more susceptible to serious or even fatal outcomes.

Due to the possibility of severe hypersensitivity reactions after administration, post-procedure observation of the patient is recommended.

Preparedness for institution of emergency measures is necessary for all patients. To permit immediate countermeasures to be taken in emergencies, appropriate medicines, an endotracheal tube and respirator should be ready at hand.

Premedication with a corticosteroid regimen may be considered in patients with an increased risk of acute allergy-like reactions, patients with a previous moderate or severe acute reaction, asthma or allergy requiring medical treatment.

Pretesting

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 reactions.

Thyroid dysfunction

Particularly careful risk/benefit judgement is required in patients with known or suspected hyperthyroidism or goitre, as iodinated contrast media may induce hyperthyroidism or thyreotoxic crisis in these patients. Iodinated contrast media should not be given to patients with manifest hyperthyroidism. Testing of thyroid function prior to ULTRAVIST administration and preventive thyreostatic medication may be considered in patients with known or suspected hyperthyroidism.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration to adult and paediatric patients. Evaluate the potential risk of hypothyroidism in patients with known or suspected thyroid diseases before use of iodinated contrast media.

In 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 an exposure to excess iodine may cause hypothyroidism, possibly requiring treatment.

CNS disorders

Patients with CNS disorders may be at increased risk of seizures and neurological complications in relationship to ULTRAVIST administration. Neurological complications are more frequent in cerebral angiography and related procedures.

Caution should be exercised in situations in which there may be a reduced seizure threshold, such as a previous history of seizures, intrathecal administration, alcoholism, drug addiction and the use of certain concomitant medication.

Factors such as brain tumours and cerebrovascular ischaemia, which increase blood-brain barrier permeability, facilitate the passage of the contrast medium into cerebral tissue, possibly leading to CNS reactions.

Hydration

Adequate hydration status must be assured in all patients before intravascular or intrathecal ULTRAVIST administration in order to minimise the risk of Post-Contrast Acute Kidney Injury (PC-AKI) (see also section 4.4 Special warnings and Precautions for Use, Use in renal impairment). This applies especially to patients with multiple myeloma, diabetes mellitus, polyuria, oliguria, hyperuricemia, as well as to newborns, infants, small children and elderly patients.

Adequate hydration status must be assured in renally impaired patients. However, prophylactic IV hydration in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73 m^2) is not recommended as additional renal safety benefits have not been established. In patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and concomitant cardiac conditions, prophylactic IV hydration can lead to increased serious cardiac complications. Refer to Section 4.2 Dosage and method of administration, 'Patients with renal impairment', Section 4.4 Special warnings and precautions for use, 'Use in renal impairment' and 'Cardiovascular disease' and Section 4.8 Adverse effects (undesirable effects), 'Adverse drug reactions from post-marketing spontaneous reports'.

Anxiety

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 minimise the state of anxiety in such patients.

Intravascular Use

Use in renal impairment

In patients with impaired renal function, the plasma half-life of iopromide is prolonged according to the reduced glomerular filtration rate. Therefore, caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, combined renal and cardiac disease, or anuria, particularly when large doses are administered.

Post-Contrast Acute Kidney Injury (PC-AKI), presenting as a transient impairment of renal function, may occur after intravascular administration of ULTRAVIST. Acute renal failure may occur in some cases.

Risk factors include, for example:

- pre-existing renal insufficiency (see Section 4.2 Dose and method of administration, Use in renal impairment)
- dehydration (see Section 4.4 Special warnings and precautions for use, Hydration)
- diabetes mellitus
- multiple myeloma / paraproteinemia
- gout
- age over 70 years
- concurrent administration of nephrotoxic drugs
- repetitive and/or large doses of ULTRAVIST

Patients with moderate to severe (eGFR 44-30 mL/min/1.73 m^2) or severe renal impairment (eGFR <30 mL/min/1.73 m2) are at increased risk of PC-AKI with intra-arterial contrast administration and first pass renal exposure.

Patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) are at increased risk of PC-AKI with intra-venous or intra-arterial contrast administration with second pass renal exposure (see subsection Hydration in Section 4.4 Special warnings and precautions for use).

Adequate hydration must be ensured in all patients who receive ULTRAVIST administration.
Patients on dialysis, if without residual renal function, may receive ULTRAVIST for radiological procedures as iodinated contrast media are cleared by the dialysis process.

In the case of severe renal insufficiency the coexistence of severe hepatic dysfunction can seriously delay contrast medium excretion. Haemodialysis should be used only if clinically indicated.

Cardiovascular disease

Patients with significant cardiac disease or severe coronary artery disease are at an increased risk of developing clinically relevant haemodynamic changes and arrhythmia.

In patients with valvular disease and pulmonary hypertension, contrast medium administration may lead to pronounced haemodynamic changes. Reactions involving ischaemic ECG changes and major arrhythmia are more common in older patients and in those with pre-existing cardiac disease.

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

Intravascular injection of ULTRAVIST may precipitate pulmonary oedema in patients with heart failure.

Pheochromocytoma

Patients with pheochromocytoma may be at increased risk to develop a hypertensive crisis. Administration of radiopaque materials to patients with known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such a procedure outweigh the considered risks, the procedure may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available. These patients should be monitored very closely during contrast enhanced procedures. Premedication with alpha-receptor blockers is recommended.

Myasthenia gravis

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

Thromboembolic events

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both non-ionic and ionic contrast media. Exercise care when performing venography in patients with suspected thrombosis, phlebitis, severe ischaemic disease, local infection, venous thrombosis or a totally obstructed venous system. Avoid angiography whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

A property of non-ionic contrast media is the low interference with normal physiological functions. As a consequence of this, non-ionic contrast media have less anticoagulant activity *in vitro* than ionic media. Numerous factors in addition to the contrast medium, 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.

Therefore, when performing vascular catheterisation procedure one should be aware of this and pay meticulous attention to the angiographic technique and flush the catheter frequently with physiological saline (if possible with the addition of heparin) and minimise the length of the procedure so as to minimise the risk of procedure-related thrombosis and embolism.

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

Patients with autoimmune disorders

Cases of severe vasculitis or Stevens-Johnson-like syndrome have been reported in patients with pre-existing autoimmune disorders.

Cerebral angiography

Use caution in patients with extreme senility, advanced atherosclerosis or severe hypotension; the procedure may be hazardous in subarachnoid haemorrhage and in migraine (because of ischaemic complications).

Peripheral angiography

Pulsation should be present in the artery to be injected; in thromboangitis obliterans (Buerger's Disease) or ischaemia associated with ascending infection, angiography should be performed with extreme caution, if at all.

Intrathecal use

Care is needed in patients with a seizure history due to an increased risk for seizures in relationship to intrathecal ULTRAVIST administration. Preparedness for institution of anti-convulsive measures is recommended.

The majority of adverse events after myelography occur some hours after administration. During this period observation is advisable.

Patients with a history of epilepsy and receiving anticonvulsant therapy should be maintained on anticonvulsant therapy when receiving the contrast medium intrathecally.

ULTRAVIST injection is not indicated for use in thoracic, cervical or total columnar myelography, nor for cerebral ventriculography and cisternography as there are insufficient data to support its use in these indications.

The safety and effectiveness of ULTRAVIST have not been established in children for intrathecal use.

Use in paediatrics

Paediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, 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 paediatric patients have not been established. Caution should be exercised in selecting the dose.

In 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 an exposure to excess iodine may cause hypothyroidism, possibly requiring treatment.

Effects on laboratory tests

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORM OF INTERACTIONS

ULTRAVIST must not be mixed with any other medicinal products to avoid the risk of possible incompatibilities.

Metformin (biguanides)

In patients with acute kidney failure, or severe chronic kidney disease, metformin 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 treated with metformin may be at an increased risk of developing lactic acidosis, especially those with prior renal impairment (see section 4.4 Special Warnings and Precautions for Use, subsection Use in renal impairment).

Neuroleptics and Antidepressants

Concomitant use of neuroleptics and antidepressants may reduce the seizure threshold, thus increasing the risk of a contrast medium related reaction.

Beta-blockers

Patients who experience hypersensitivity reactions while taking a beta-blocker may be resistant to treatment effects of beta agonists (see also section 4.2, Special Warnings and Precautions for Use, Hypersensitivity Reactions).

Patients on beta-blockers may be unresponsive to the usual doses of adrenalin used to treat allergic reactions. Because of the risk of hypersensitivity reactions, use caution when administering iodinated contrast agents to patients taking beta-blockers.

Interleukin-2

Previous treatment (up to several weeks) with Interleukin-2 is associated with an increased risk for delayed reactions to ULTRAVIST.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Long term animal studies have not been performed to evaluate carcinogenic potential or effects on fertility. Iopromide was not genotoxic in a series of studies for gene mutations (Ames test) and chromosomal damage (*in vivo* mouse micronucleus assay and in an *in vivo* mouse dominant lethal assay).See also section 5.3.

Use in pregnancy - Category B2

Adequate and well-controlled studies in pregnant women have not been conducted. Embryotoxicity including teratogenicity studies have been performed in rats and rabbits at doses up to 3.7 g I/kg body weight. These studies did not indicate an increased risk of adverse effects to the foetus following the intended diagnostic use in humans.

Before administration to women during pregnancy, the benefit to the patient should be carefully weighed against the possible risk to the foetus. ULTRAVIST should be used only if, in the judgement of the clinician, its use is deemed essential to the welfare of the patient. Generally, radiography of the abdomen is considered to be contraindicated during pregnancy.

Use in lactation

The safety of ULTRAVIST for nursed infants has not been investigated. Contrast media are poorly excreted in human breast milk. Harm to the nursed infant is not likely to occur. See also Section 4.4 Special Warnings and Precautions for Use, subsection 'Thyroid dysfunction' and 'Use in paediatrics'.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Because of the risk of delayed adverse reactions, as a precaution, driving or operating machinery should be avoided for the first 24 hours after intrathecal as well as after intravascular administration of contrast media.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The overall safety profile of ULTRAVIST is based on data obtained in pre-marketing studies in more than 3900 patients and post-marketing studies in more than 74,000 patients, as well as data from spontaneous reporting and the literature.

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

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

Tabulated list of adverse reactions

The adverse drug reactions observed with ULTRAVIST are represented in the table below. They are classified according to System Organ Class (MedDRA version 13.0). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions. Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention:
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)

Table 1: Adverse drug reactions (ADRs) reported in clinical trials

System organ class	Common	Uncommon	Rare
Immune system disorders		Hypersensitivity / anaphylactoid reactions (anaphylactoid shock*, respir-atory arrest*, bronchospasm*, laryngeal* / pharyngeal* / face oedema, tongue oedema, laryngeal / pharyngeal spasm, asthma*, conjunctivitis, lacrimation, sneezing, cough, mucosal oedema, rhinitis, hoarseness, throat irritation, urticaria, pruritus, angioedema)	
Psychiatric disorders			Anxiety

System organ class	Common	Uncommon	Rare
Nervous system disorders	Dizziness Headache Dysgeusia	Vasovagal reactions Confusional state Restlessness Paraesthesia / hypoaesthesia Somnolence	
Eye disorders	Blurred / disturbed vision		
Cardiac disorders	Chest pain / discomfort	Arrhythmia*	Cardiac arrest* Myocardial ischaemia* Palpitations
Vascular disorders	Hypertension Vasodilatation	Hypotension*	
Respiratory, thoracic and mediastinal disorders		Dyspnoea*	
Gastrointestinal disorders	Vomiting Nausea	Abdominal pain	
General disorders and administration site conditions	Pain Injection site reactions (various kinds, e.g. pain, warmth, oedema, inflammation and soft tissue injury in case of extravasation) Feeling hot		

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

Table 2: Adverse drug reactions reported in a post-marketing surveillance study

System organ class	Common	Uncommon	Rare
Cardiac disorders			Palpitations
General disorders and administration site conditions	Feeling hot	Oedema	

The above additional adverse drug reactions were reported in a post-marketing surveillance study conducted in over 74,000 patients from 25 countries.

Adverse drug reactions from Post-Marketing Spontaneous Reports

Endocrine disorders
Thyrotoxic crisis, thyroid disorder

Nervous system disorders
Coma*, cerebral ischaemia / infarction*, stroke*, brain oedema[a]*, convulsion*, transient cortical blindness[a], loss of consciousness, agitation, amnesia, tremor, speech disorders, paresis / paralysis

Ear and labyrinth disorders
Hearing disorders

Cardiac disorders
Myocardial infarction*, cardiac failure*, bradycardia*, tachycardia, cyanosis*

Vascular disorders
Shock*, thromboembolic events[a], vasospasm[a]

Respiratory, thoracic and mediastinal disorders
Pulmonary oedema*, respiratory insufficiency*, aspiration*

Gastrointestinal disorders
Dysphagia, salivary gland enlargement, diarrhoea

Skin and subcutaneous tissue disorders:
Severe cutaneous reactions: Toxic epidermal necrolysis (TEN)/Lyell syndrome*, Stevens-Johnson syndrome (SJS)*, Drug reaction with eosinophilia and systemic symptoms (DRESS), Acute generalised exanthematous pustulosis (AGEP), rash, erythema, hyperhydrosis

Musculoskeletal, connective tissue and bone disorders:
Compartment syndrome in case of extravasation[a]

Renal and urinary disorders:
Renal impairment[a], acute renal failure[a]

General disorders and administration site conditions:
Malaise, chills, pallor, pain, warmth, oedema, inflammation

Investigations:
Body temperature fluctuation

** life-threatening and/or fatal cases have been reported*
[a] intravascular use only

In addition to the adverse drug reactions (ADRs) listed above, the following ADRs have been reported with:

Intrathecal use: Chemical meningitis and meningism at an unknown frequency.
Use for ERCP: Elevation of pancreatic enzyme levels and pancreatitis at an unknown frequency.

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

Description of selected adverse reactions

Based on experience with other non-ionic contrast media, the following undesirable effects, may occur with intrathecal use in addition to the undesirable effects listed above:
Psychosis, neuralgia, paraplegia, aseptic meningitis, back pain, pain in extremities, micturition disorder, EEG abnormal.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
In Australia: http://www.tga.gov.au/reporting-problems.
In New Zealand : https://nzphvc.otago.ac.nz/reporting/

4.9 OVERDOSE

Results from acute toxicity studies in animals do not indicate a risk of acute intoxication following use of ULTRAVIST.

Intravascular overdose

Symptoms may include fluid and electrolyte imbalance, renal failure, cardiovascular and pulmonary complications.

In case of inadvertent intravascular overdosage it is recommended to monitor fluids, electrolytes and renal function. Treatment of overdose should be directed toward the support of vital functions.

ULTRAVIST is dialysable.

Intrathecal overdose

Serious neurological complications may occur. Close monitoring is recommended in case of inadvertent intrathecal overdosage.

For information on the management of overdose, contact:
Australia: The Poison Information Centre on 131126 (Australia)
New Zealand: The National Poisons Centre on 0800 POISON (0800 764766)

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The contrast-giving substance in the ULTRAVIST formulation is iopromide, a non-ionic, water-soluble derivative of triiodinated isophthalic acid with a molecular weight of 791.12 in which the firmly bound iodine absorbs the X-rays.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

General information

Iopromide behaves in the organism like other highly hydrophilic biologically inert, renally excreted compounds (e.g. mannitol or inulin).

Absorption and distribution

Following intravenous administration, plasma concentrations of iopromide decline rapidly due to distribution into the extracellular space and subsequent elimination.

The total distribution volume at steady state is about 16 L corresponding roughly to the volume of the extracellular space. Protein binding is negligible (about 1%). There is no indication that iopromide crosses the intact blood-brain-barrier. A small amount crossed the placental barrier in animal studies (≤ 0.3% of the dose were found in rabbit fetuses).

Following intravenous administration (infusion over 15 minutes), maximum serum concentrations of total iodine following a low dose of about 15 g iodine (118 mmol) were about 1.39 ± 0.242 g/L (10.9 ± 1.90 mmol/L) and following a high dose of 80 g iodine (630 mmol), were about 7.06 ± 1.13 g/L (55.6 ± 8.89 mmol/L), at 15 min after start of infusion.

Following intrathecal administration, maximum iodine concentrations of 4.5% of the administered dose per total plasma volume were observed after 3.8 hours.

Following administration in the biliary and/or pancreatic duct during Endoscopic Retrograde Cholangiopancreaticography (ERCP), iodinated contrast agents are systemically absorbed and reach peak plasma concentrations between 1 and 4 h post administration. Maximum serum iodine levels following a mean dose of about 7.3 g iodine (57.4 ± 22.8 mmol) were about 85.2 µmol/L 4 hours after administration of ULTRAVIST 300. This value is about factor 40 lower than the maximum serum levels reached after respective intravenous doses. During the same time period, free serum iodine levels rose to about 5.42 µmol/L.

Metabolism

Iopromide is not metabolised.

Excretion

The terminal elimination half-life of iopromide is approximately 2 hours, irrespective of the dose.

In the dose range tested, the mean total clearance of iopromide following intravenous administration of a low (15 g iodine) and a high (80 g iodine) dose amounts to mean values between 109.5 ± 11.0 mL/min and 103 ± 13.3 mL/min, respectively. Total clearance is very similar to the renal clearance of 104 ± 12.7 mL/min (low dose) and 100 ± 17.8 mL/min (high dose). Thus, excretion of iopromide is almost exclusively renal. Only about 2% of the dose administered is excreted via the faecal route within 3 days.

Approximately 60% of the dose is excreted via urine within 3 hours after intravenous administration. In the mean ≥ 93% of dose was recovered within 12 hours. Excretion is essentially complete within 24 hours.

After intrathecal administration for lumbar myelography, elimination of iopromide from plasma is prolonged with a terminal elimination half-life of 14.9 ± 17 hours. Approximately 78 ± 15% of iopromide is excreted renally within 72 hours.

Following administration into the biliary and/or the pancreatic duct for ERCP, urinary iodine serum concentrations returned to pre-dose levels within 7 days.

Linearity/non-linearity

The pharmacokinetic parameters of iopromide in humans change dose proportionally (e.g. C_{max}, AUC) or are dose independent (e.g. V_{ss}, $t_{1/2}$).

Characteristics in special patient populations

Patients with renal impairment

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

The plasma clearance was reduced to 49.4 mL/min/1.73 m2 (CV = 53%) in mildly and moderately impaired patients (80 > CL_{CR} > 30 mL/min/1.73 m^2) and to 18.1 mL/min/1.73 m^2 (CV = 30%) in severely impaired patients not depending on dialysis (CL_{CR} = 30 – 10 mL/min/ 1.73 m^2).

The mean terminal half-life is 6.1 hours (CV = 43%) in mildly and moderately impaired patients (80 ≥ CL_{CR} > 30 mL/min/1.73 m^2) and 11.6 hours (CV = 49%) in severely impaired patients not depending on dialysis (CL_{CR} = 30 – 10 mL/min/1.73 m^2).

The amount recovered in urine within 6 h post dose was 38% in mildly to moderately impaired patients and 26% in severely impaired patients, compared to more than 83% in healthy volunteers. Within 24 h post dose the recovery was 60% in mIdly to moderately and 51% in severely impaired patients, compared to more than 95% in healthy volunteers.

Iopromide can be eliminated by haemodialysis. Approximately 60% of the iopromide dose is removed during a 3 hours dialysis.

Patients with hepatic impairment

Elimination is not affected by impaired liver function because iopromide is not metabolised and only 2% of the dose is excreted in the faeces.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Long term animal studies have not been performed to evaluate effects on fertility. Iopromide was not genotoxic in a series of studies for gene mutations (Ames test) and chromosomal damage (in vivo mouse micronucleus assay and in an in vivo mouse dominant lethal assay).

Carcinogenicity

Long term animal studies have not been performed to evaluate carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ULTRAVIST also contains trometamol, sodium calcium edetate, dilute hydrochloric acid (10%) (for pH adjustment) and water for injections.

6.2 INCOMPATIBILITIES

ULTRAVIST must not be mixed with any other medicinal products to avoid the risk of possible incompatibilities.

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Protect from light and secondary X-rays.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type:
Vials: Type I clear glass
Bottles:Type II clear glass

ULTRAVIST 240
Each mL of injection contains 499 mg iopromide (equivalent to 240 mg iodine)

Glass vials of 10 mL: Packs of 1 x 10 mL vial, 10 x 10 mL vials
Glass bottles of 50 mL: Packs of 10 x 50 mL bottles

ULTRAVIST 300
Each mL of injection contains 623 mg iopromide (equivalent to 300 mg iodine)

Glass vials of 20 mL: Packs of 10 x 20 mL vials
Glass bottles of 50 mL, 75 mL and 100 mL: Packs of 10 x 50 mL, 75 mL or 100 mL bottles

ULTRAVIST 370
Each mL of injection contains 769 mg iopromide (equivalent to 370 mg iodine)

Glass vials of 30 mL: Packs of 10 x 30 mL vials
Glass bottles of 50 mL, 75 mL, 100 mL and 200 mL: Packs of 1 x 100 mL or 200 mL bottles, Packs of 10 x 50 mL, 75 mL or 100 mL bottles

Not all presentations are marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia and New Zealand, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

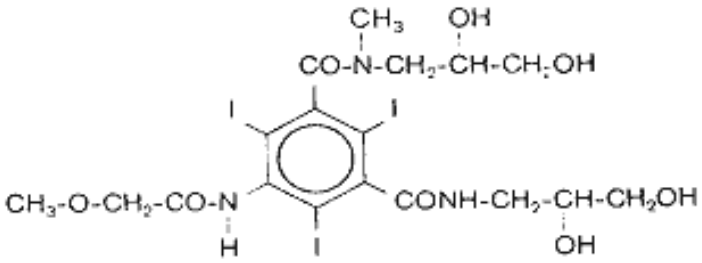
Pharmacotherapeutic group: Water soluble, nephrotropic, low-osmolar X-ray contrast media

ATC code: V08AB05

ULTRAVIST is a non-ionic contrast medium containing iopromide as the active ingredient. Iopromide is a triiodinated, non-ionic, water-soluble X-ray contrast medium.

Chemical structure

Chemically, iopromide is N,N'-Bis(2,3-dihydroxypropyl)-2,4,6-tri-iodo-5-(2-methoxyacetamido)-N-methylisophthalamide and has the following structural formula:



Molecular weight: 791.12

CAS No. 73334-07-3

Physicochemical properties

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

Property	ULTRAVIST 240 240 mg I/mL	ULTRAVIST 300 300 mg I/mL	ULTRAVIST 370 370 mg I/mL
Viscosity (mPa.s or cP)			
at 20°C	4.9	8.9	22.0
at 37°C	2.8	4.7	10.0
Osmolality at 37°C (osm/kg H_2O)	0.48	0.59	0.77
Osmolarity at 37°C (osm/L solution)	0.36	0.43	0.49
Osmotic pressure			
Density (g/mL) 20°C	1.262	1.330	1.409
Density (g/mL) 37°C	1.255	1.322	1.399

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).

7. MEDICINE SCHEDULE

Australia: Not Scheduled
New Zealand General Sales Medicine

8. SPONSOR

Bayer Australia Ltd
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
www.bayer.com.au

Bayer New Zealand Limited
PO Box 2825
Shortland Street
Auckland 1140
Free phone 0800 229 376

9. DATE OF FIRST APPROVAL

ULTRAVIST 240: 10 June 1999
ULTRAVIST 300: 8 September 1988
ULTRAVIST 370: 8 September 1988

10. DATE OF REVISION OF THE TEXT

25 January 2022

Summary table of changes

Section changed	Summary of new information
4.4	Additional precautionary information under Thyroid dysfunction.
4.8	Update to include severe cutaneous reactions reported during post-marketing surveillance.
8	Update to New Zealand Sponsor Details