APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ULTRAVIST 300 20 mL, ULTRAVIST 300 50 mL, ULTRAVIST 300 75 mL,
ULTRAVIST 300 100 mL, ULTRAVIST 300 125 mL, ULTRAVIST 300 200 mL,
ULTRAVIST 300 500 mL
ULTRAVIST 370 50 mL, ULTRAVIST 370 100 mL, ULTRAVIST 370 125 mL,
ULTRAVIST 370 200 mL, ULTRAVIST 370 500 mL
Solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ULTRAVIST 300: 1 mL contains 623 mg iopromide (equivalent to 300 mg iodine).
ULTRAVIST 370: 1 mL contains 769 mg iopromide (equivalent to 370 mg iodine).
Sugar free
Excipients with known effect
Each 1 mL contains 0.000534 mmol (equivalent 0.0123 mg) of sodium. Please see section 4.4 for further information.

For a full list of excipients, refer to section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion
Clear, very slightly brown, very slightly brownish-yellow or very slightly yellow, sterile, pyrogen-free solution.
The physico-chemical properties of ULTRAVIST at the concentration listed below are:

	ULTRAVIST 300	**ULTRAVIST 370**
Iodine concentration (mg/mL)	**300**	**370**
Iodine content (g) per		
Vial of 20 mL	6,0	-
Bottle of 50 mL	15,0	18,5
Bottle of 75 mL	22,5	-
Bottle of 100 mL	30,0	37,0
Bottle of 125 mL	37,5	46,25
Bottle of 200 mL	60,0	74,0
Bottle of 500 mL	150,0	185,0
Contrast medium concentration (mg/mL)	623	769

	ULTRAVIST 300	**ULTRAVIST 370**
Contrast medium content (g) per		
Bottle of 50 mL	31,2	38,4
Bottle of 100 mL	62,3	76,9
Bottle of 125 mL	78,0	96,0
Bottle of 200 mL	124,6	153,8
Bottle of 500 mL	312,0	384,0
Viscosity (mPa.s or cP)		
At 20 °C	8,9	22,0
At 37 °C	4,7	10,0
Osmotic pressure at 37 °C		
(MPa)	1,59	2,02
(atm)	15,7	19,9
Osmolality at 37 °C (osm/kg H2O)	0,59	0,77

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

ULTRAVIST 300
Contrast enhancement in computerised tomography, arteriography and venography including intravenous/intraarterial digital subtraction angiography; intravenous urography, visualisation of body cavities (e.g. arthrography). **Not for intrathecal use.**

ULTRAVIST 370
Contrast enhancement in computerised tomography, arteriography including intravenous digital subtraction angiography; and especially angiocardiography; intravenous urography, visualisation of body cavities (e.g. arthrography). **Not for intrathecal use.**

4.2 Posology and method of administration:

General information
Contrast media which are warmed to body temperature before administration are better tolerated and can be injected more easily because of reduced viscosity. For additional instructions, see section 6.6

Posology

Single dose use. Discard unused portions.
Dosage for intravascular use

The dosage may vary depending on the age, weight, cardiac output and general condition of the patient and also on the clinical problem, examination technique and the region to be investigated. 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 kg body weight as indicated below.

Generally, doses of up to 1,5 g iodine per kg body weight may be used.

Recommended doses for single injections:

Conventional angiography:

Aortic arch angiography	50 to 80 mL ULTRAVIST 300
Selective angiography	6 to 15 mL ULTRAVIST 300
Thoracic aortography	50 to 80 mL ULTRAVIST 300/370
Abdominal aortography	40 to 60 mL ULTRAVIST 300
Arteriography	
Upper extremities	8 to 12 mL ULTRAVIST 300
Lower extremities	20 to 30 mL ULTRAVIST 300
Angiocardiography	
Cardiac ventricles	40 to 60 mL ULTRAVIST 370
Intracoronary	5 to 8 mL ULTRAVIST 370
Venography	
Upper extremities	15 to 30 mL ULTRAVIST 300
Lower extremities	30 to 60 mL ULTRAVIST 300

Intravenous digital subtraction angiography:
The intravenous injection of 30 to 60 mL ULTRAVIST 300/370 as a bolus (flow rate: 8 to 12 mL/ second into the cubital vein; 10 to 20 mL/ second into the vena cava) is only recommended for contrast demonstrations of great vessels of the trunk. The amount of contrast medium remaining in the veins can be reduced and diagnostically used by injecting 20 to 40 mL isotonic sodium chloride solution as a bolus immediately afterwards.

Adults: 30 to 60 mL ULTRAVIST 300/370

Intraarterial digital subtraction angiography:
The dosages and concentrations used in conventional angiography can be reduced for intraarterial digital subtraction angiography.

Computerised tomography:
Whenever possible, ULTRAVIST should be injected as an intravenous 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 to 6 minutes to guarantee a relatively constant – though not maximum – blood level. Spiral computerised tomography in single, but especially in multi-slice technique, allows the rapid acquisition of a volume of data during single breath hold. To optimise the effect of the intravenous

administered bolus (80 to 150 mL ULTRAVIST 300) in the region of interest (peak, time and duration of enhancement), the use of an automatic power injector and bolus tracking is strongly recommended.

- Whole body computerised tomography

In 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 computerised tomography

Adults:		
	ULTRAVIST 300:	1,0 to 2,0 mL/kg body weight
	ULTRAVIST 370:	1,0 to 1,5 mL/kg body weight

Intravenous urography:
The physiologically poor concentrating ability of the still immature nephron of infantile kidneys demands relatively high doses of contrast medium.
The following dosages are recommended:

Neonates (< 1 month)	1,2 g I/kg body weight	= 4,0 mL/kg body weight ULTRAVIST 300
		= 3,2 mL/kg body weight ULTRAVIST 370
Infants (1 month to 2 years)	1,0 g I/kg body weight	= 3,0 mL/kg body weight ULTRAVIST 300
		= 2,7 mL/kg body weight ULTRAVIST 370
Children (2 to 11 years)	0,5 g I/kg body weight	= 1,5 mL/kg body weight ULTRAVIST 300
		= 1,4 mL/kg body weight ULTRAVIST 370
Adolescents and adults	0,3 g I/kg body weight	= 1,0 mL/kg body weight ULTRAVIST 300
		= 0,8 mL/kg body weight ULTRAVIST 370

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

Children (2 to 11 years)	0,5 g I/kg body weight	= 1,5 mL/kg body weight ULTRAVIST 300
		= 1,4 mL/kg body weight ULTRAVIST 370
Adolescents and adults	0,3 g I/kg body weight	= 1,0 mL/kg body weight ULTRAVIST 300
		= 0,8 mL/kg body weight ULTRAVIST

		370

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

- Filming times:

When the above dosage guidelines are observed and ULTRAVIST 300/370 is administered over 1 to 2 minutes, the renal parenchyma is usually highly opacified 3 to 5 minutes and the renal pelvis with the urinary tract 8 to 15 minutes 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 to 3 minutes after administration of the contrast medium. In neonates, infants and patients with impaired renal function later films may improve visualisation of the urinary tract.

Dosage for use in other body cavities:

During arthrography and hysterosalpingography 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.

Recommended doses for single examinations:

Arthrography: 5 to 15 mL ULTRAVIST 300/370.
ERCP: Dosage depends generally on clinical question and size of structure to be imaged.
ERCP must not be performed in acute pancreatitis.
Other: Dosage depends generally on clinical question and size of structure to be imaged.

Special populations

Neonates, infants and children:

Young infants (age < 1 year) and especially newborn are susceptible to electrolyte imbalance and haemodynamic 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):

In a clinical study, no differences in pharmacokinetics of iopromide were observed between elderly (aged 65 years and above) and younger patients. Therefore, no specific recommendation for a dosage adjustment is given for elderly patients besides those described in subsection “Dosage regimen”.

Patients with renal impairment:

Since ULTRAVIST is excreted almost exclusively in an unchanged form via the kidneys, the elimination of ULTRAVIST 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 section 4.4 and 5.2).

Patients with hepatic impairment:

Elimination of ULTRAVIST is not affected by impaired liver function as only about 20 % of the dose is eliminated via faeces and ULTRAVIST is not metabolized. No dosage adjustment is considered necessary in patients with hepatic impairment.

Method of Administration
For intravascular use and use in body cavities.

4.3 Contraindications

- Uncontrolled Hyperthyroidism (see section 4.4).
- Not to be administered to patients who are allergic to iodine.
- Hysterosalpingography must not be performed during pregnancy or in the presence of acute inflammatory processes in the pelvic cavity.
- The safety of ULTRAVIST in pregnancy has not been established. ULTRAVIST should not be used during pregnancy.
- ERCP (endoscopic retrograde cholangiopancreatography) is contraindicated in acute pancreatitis.
- Serum creatinine indicating moderate to severe renal impairment (see section 4.4).
- ULTRAVIST 300 and 370 are not indicated for intrathecal use.

4.4 Special warnings and precautions for use

Fatal reactions have been associated with the administration of ULTRAVIST. It is therefore of the utmost importance that a course of action be carefully planned in advance for the treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of a severe reaction. Patients should be observed for a possible severe reaction during and for at least 30 to 60 minutes after administration. In rare cases delayed reactions may occur (after hours to days).

For all indications

The following warnings and precautions apply to any mode of administration of ULTRAVIST; however, the risks mentioned are higher in intravascular administration.

Hypersensitivity reactions
ULTRAVIST can be associated with anaphylactic/hypersensitivity or other idiosyncratic reactions characterised by cardiovascular, respiratory and cutaneous manifestations such as mild respiratory distress, reddening of the skin (erythema), urticaria, itching or facial oedema. Serious events such as

angioedema, subglottic oedema, bronchospasm and allergic shock are rare.

Anaphylactic/anaphylactoid reactions ranging from mild to severe reactions including shock are possible. Most of these reactions occur within 30 minutes of administration. However, delayed reactions (after hours to days) may occur (see section 4.8).

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 hypersensitivity reactions to ULTRAVIST while simultaneously taking beta blockers may be resistant to treatment effects of beta agonists (see also section 4.5).

Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to iodine or to radiographic media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions.

Patients with bronchial asthma are at special risk of having bronchospasms or a hypersensitivity reaction.

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.
In patients with an allergic disposition, increased risk of acute allergy-like reactions, patients with a previous moderate or severe acute reaction, allergy requiring medical treatment, known hypersensitivity to iodinated contrast media or a history of asthma, premedication with antihistamines and/or glucocorticoids may be considered.

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 and thyrotoxic crisis in these patients.

Testing of thyroid function prior to ULTRAVIST administration and/or preventive thyroid medication may be considered in patients with known or suspected hyperthyroidism.

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.

Central nervous system disorders
Particular care should be paid to the intravascular administration of contrast media in patients with acute cerebral infarction, acute intracranial haemorrhage, and other conditions involving blood brain barrier damage, cerebral oedema or acute demyelination. Intracranial tumours or metastases and a history of epilepsy may increase the incidence of convulsive seizures after administration of ULTRAVIST. Neurological symptoms due to cerebrovascular diseases, intracranial tumours or metastases, degenerative or inflammatory pathologies may be exacerbated by ULTRAVIST administration.
Vasospasm and subsequent cerebral ischaemic phenomena may be caused by intraarterial injections of ULTRAVIST. Patients with symptomatic cerebrovascular diseases, recent stroke or frequent transient ischaemic attacks have an increased risk of neurological complications.

Patients with CNS disorders may be at increased risk to have 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 reduced seizure threshold, such as a previous history of seizures and the use of certain concomitant medication.
Factors 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 contrast medium administration (see also subsection Acute Kidney Injury). This applies especially to patients with multiple myeloma, diabetes mellitus, polyuria, oliguria, hyperuricaemia or patients using diuretics as well as to 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 subsection Acute Kidney Injury, Cardiovascular disease, and section 4.8.

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.

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.

Intravascular use

Acute Kidney Injury

Post-Contrast Acute Kidney Injury (PC-AKI) presenting as a transient impairment of renal function, may occur after intravascular administration of ULTRAVIST. Temporary renal failure may occur in rare cases.
Preventive measures against acute renal failure following contrast medium administration include:

- Identifying high-risk patients, e.g. patients with a history of renal disease, pre-existing renal insufficiency (see section 4.2 subheading Patients with renal impairment), previous renal failure after contrast medium administration, diabetes mellitus with nephropathy, volume depletion, multiple myeloma, age greater than 60 years, advanced vascular disease, paraproteinaemia, severe and chronic hypertension, gout, patients receiving large or repeated doses.
- Ensuring adequate hydration in all patients before contrast medium administration, preferably by maintaining intravascular infusion before and after the procedure and until the contrast medium has been cleared by the kidneys (see section 4.4).
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, major surgery, etc., until the contrast medium has been cleared.
- Postponing a new contrast medium examination until renal function returns to pre-examination levels.

Patients with moderate to severe (eGFR 44-30 mL/min/1.73 m2) or severe renal impairment (eGFR <30 mL/min/1.73 m2) are at increased risk of Post-Contrast Acute Kidney Injury (PC-AKI) with intra-arterial contrast administration and first pass renal exposure. Patients with severe renal impairment (eGFR <30 mL/min/1.73 m2) are at increased risk of PC-AKI with intra-venous or intra-arterial contrast administration with second pass renal exposure (see subsection Hydration).

Patients on dialysis, if without residual renal function, may receive ULTRAVIST for radiological procedures as iodinated contrast media are cleared by the dialysis process.

Cardiovascular disease
Patients with significant cardiac disease or severe coronary artery disease are at an increased risk of developing clinically relevant haemodynamic changes and dysrhythmia. In patients with valvular disease and pulmonary hypertension, contrast medium administration may lead to pronounced haemodynamic changes. Reactions involving ischaemic ECG changes and major dysrhythmia are more common in older patients and in those with pre-existing cardiac disease.
The intravascular injection of contrast media may precipitate pulmonary oedema in patients with heart failure.

Phaeochromocytoma
Patients with phaeochromocytoma may develop a severe (occasionally uncontrollable) hypertensive crisis following intravascular ULTRAVIST use.

Myasthenia gravis
The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis.

Thromboembolic events
A property on non-ionic contrast media is the low interference with normal physiological function. 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 a 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.

Biguanides (metformin)
The presence of renal damage in diabetic patients is one of the factors predisposing to renal impairment following contrast media administration. This may precipitate lactic acidosis in patients who are taking biguanides. As a precaution, biguanides should be stopped 48 hours prior to the contrast agent examination and reinstated only after control of renal function has been regained (see section 4.5).

Severe liver dysfunction
In the case of severe renal insufficiency, the coexistence of severe hepatic dysfunction can seriously delay contrast medium excretion, possibly necessitating haemodialysis.

Myeloma and paraproteinaemia
Myeloma or paraproteinaemia may predispose to renal impairment following ULTRAVIST administration. Adequate hydration is mandatory.

Use in other body cavities
ERCP must not be performed in acute pancreatitis.

Important information about some ingredients
ULTRAVIST contains less than 1 mmol (23 mg) sodium per dose (based on the average amount given to a 70 kg person), i.e. essentially ‘sodium-free’.

4.5 Interactions with other medicines and other forms of interactions

Biguanides (metformin)

The presence of renal damage in diabetic patients is one of the factors predisposing to renal impairment following contrast media administration. In patients with acute kidney failure or severe chronic kidney disease biguanide elimination can be reduced leading to accumulation and development of lactic acidosis. As the administration 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 subsection Hydration).

Beta blockers

Hypersensitivity reactions can be aggravated in patients on beta-blockers, particularly in people with bronchial asthma. Patients who experience hypersensitivity reactions while taking a beta-blocker may be resistant to treatment effects of beta agonists (see section 4.4).

Interleukin-2

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

Interference with diagnostic 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Adequate and well-controlled studies in pregnant women have not been conducted. It has not been sufficiently demonstrated that non-ionic contrast media such as ULTRAVIST are safe for use in pregnant patients. Radiation exposure should be avoided during pregnancy.

Lactation
Safety of ULTRAVIST in breastfeeding has not been investigated. Contrast media are poorly excreted in human breast milk.

4.7 Effects on ability to drive and use machines

Not known

4.8 Undesirable effects

a) 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 literature.
The mostly 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 oedema, pharyngeal oedema, asthma, coma, cerebral infarction, stroke, brain oedema, convulsion, arrhythmia, cardiac arrest, myocardial ischaemia, myocardial infarction, cardiac failure, bradycardia, cyanosis, hypotension, shock, dyspnoea, pulmonary oedema, respiratory insufficiency and aspiration.

b) Tabulated summary of adverse reactions

The side effects observed with ULTRAVIST are represented in the table below. They are classified according to System Organ Class. The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Side effects from clinical trials are classified according to their frequencies.

Table 1: Side effects reported during clinical trials:

System Organ Class	Common (≥ 1/100, < 1/10)	Uncommon (≥ 1/1000 and < 1/100)	Rare (< 1/1000)
Immune system disorders		Hypersensitivity /Anaphylactoid reactions (anaphylactoid shock[$]* , respiratory arrest* , bronchospasm*, laryngeal*/ pharyngeal*/ face oedema, tongue oedema[$], laryngeal/ pharyngeal spasm[$], asthma[$]*, conjunctivitis[$], lacrimation, sneezing, cough, mucosal oedema, rhinitis[$], hoarseness, throat irritation[$], urticaria, pruritus, angioedema)	
Psychiatric disorders			Anxiety
Nervous system disorders,	Dizziness, Headache, Dysgeusia	Vasovagal reactions, Confusional state, Restlessness, Paraesthesia/ hypoaesthesia, Somnolence	
Eye disorders	Blurred/disturbed vision		
Cardiac disorders	Chest pain/discomfort	Dysrhythmia*	Palpitations, cardiac arrest*, myocardial ischemia*
Vascular disorders	Hypertension, Vasodilation	Hypotension*	
Respiratory, thoracic and mediastinal disorders		Dyspnoea*	
Gastrointestinal disorders	Vomiting, Nausea	Abdominal pain	
General	Pain, Injection		

disorders and administration site conditions	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.
[$] Identified only during post marketing surveillance (frequency not known).

ERCP
In addition to the undesirable effects listed above, the following undesirable effects may occur with use for ERCP: Elevation of pancreatic enzyme levels (common), pancreatitis (rare).

Post-marketing data:
The side effects identified during post-marketing surveillance, and for which a frequency is not known are as follows:

System Organ Class	
Endocrine disorders	Thyrotoxic crisis, Thyroid disorder
Nervous system disorders	Coma*, cerebral ischaemia/ infarction*, stroke*, brain oedema* [a], convulsions*, 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	Bullous conditions (e.g. Stevens-Johnson's or Lyell syndrome), 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]
Investigations	Body temperature fluctuation

***** - Life-threatening and/ or fatal cases have been reported.
[a] - Intravascular use only.

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 to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Alternatively, you can report to Bayer SafeTrack site (https://www.safetrack-public.bayer.com).

4.9 Overdosage

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 towards the support of vital functions. ULTRAVIST is dialyzable (see section 5.2).

5. PHARMACOLOGICAL ACTION

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Water-soluble, nephrotropic, low osmolar X-ray contrast media
ATC code: V08AB05

Iopromide is a non-ionic, water-soluble contrast medium with low osmotic pressure. It is a derivative of tri-iodinated isophthalic acid in which the bound iodine absorbs the X-rays.

Injection of iopromide opacifies those vessels or body cavities in the path of flow of the contrast agent, permitting radio-graphic visualisation of the internal structures until significant dilution occurs.

5.2 Pharmacokinetic properties

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 litres corresponding roughly to the volume of the extracellular space.

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 foetuses).
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 hours post administration. Maximum serum iodine levels following a mean dose of about 7,3 g iodine were about factor 40 lower compared to maximum serum levels reached after respective intravenous doses.

Metabolism

Iopromide is not metabolised. No metabolites were demonstrable in man following administration of the clinically relevant doses of iopromide.

Elimination

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 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 faecal route within 3 days.

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

Following linear 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}, $T_{½}$).

Characteristics in special patient populations

Elderly population

Middle aged patients (49 – 64 years) and elderly patients (65 – 70 years). Without significantly impaired renal function, had total plasma clearances between 74 and 114 mL/ min (middle aged group, mean 102 mL/ min) and between 72 and 110 mL/ min (elderly group, mean 89 mL/ min), which is only marginally lower than those in young healthy subjects (88 to 138 mL/ min, mean 106 mL/ min). The individual elimination half-lives were between 1,9 – 2,9 hours and 1,5 – 2,7 hours, respectively. Compared to the range of 1,4 to 2,1 hours in young healthy volunteers, terminal half-lives are similar. The minor differences correspond to the physiologically reduced glomerular filtration rate with age.

Paediatric population

Pharmacokinetics of iopromide has not been investigated in the paediatric population (see section 4.2).

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 m^2 (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 and 26 % in severely impaired patients, compared to more than 83 % in healthy volunteers. Within 24 hours post dose the recovery was 60 % in mildly 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 about 2 % of dose is excreted in the faeces.

5.3 Preclinical safety data

Preclinical data reveal no evidence of risk for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and reproduction toxicity.

Systemic toxicity

Experimental systemic tolerance studies following repeated daily intravenous and repeated weekly intrathecal administration produced no findings which object to a diagnostic administration of ULTRAVIST to humans.

Genotoxic potential, tumorigenicity

Studies into genotoxic effects (gene-, chromosomal- and genome mutation tests) *in vivo* and *in vitro* gave no indication of a mutagenic potential of ULTRAVIST.
Due to the absence of genotoxic effects and taking into account the metabolic stability, pharmacokinetics and the absence of indications of toxic effects on fast-growing tissues as well as the fact that ULTRAVIST was only administered once, there is no evident risk of a tumorigenic effect on humans.

Local tolerance and contact-sensitizing potential

Local tolerance studies following single as well as repeated intravenous administration and single intraarterial, intramuscular, paravenous, intraperitoneal, intrathecal and conjunctival administration indicated that no or only slight adverse local effects are to be expected in blood vessels, paravenous

tissue, subarachnoidal space or on the human mucosa.
Studies into contact-sensitizing effect, gave no indication of a sensitizing potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium sodium edetate,
hydrochloric acid,
trometamol and
water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

36 months (3 years)

6.4 Special precautions for storage:

For single dose use. Discard unused portion. Protect from light, heat and secondary X-rays. For shelf-life, refer to the imprint on the pack. Keep out of reach of children.
Store in the outer cartons at or below 30 °C.

6.5 Nature and contents of container

ULTRAVIST 300: Colourless vials of 20 mL with grey plastic stoppers packed in a carton containing 10 vials.
ULTRAVIST 300: Colourless bottles of 50, 75 or 100 mL with grey plastic stoppers packed in a carton containing 10 bottles
ULTRAVIST 300: Colourless bottles of 125 mL with grey plastic stoppers packed in a carton containing 5 or 10 bottles.
ULTRAVIST 300: Colourless pre-filled plastic cartridges of 75, 100 and 125 mL packed into a carton containing 1x 5 cartridges or 2 x 5 cartridges.
ULTRAVIST 300: Colourless bottles of 200 mL with grey plastic stoppers packed in a carton containing 1 or 10 bottles.
ULTRAVIST 300: Colourless bottles of 500 mL with grey plastic stoppers packed in a carton containing 1 or 8 bottles.
ULTRAVIST 370: Colourless bottles of 50 or 100 mL with grey plastic stoppers packed in a carton

containing 10 bottles.
ULTRAVIST 370: Colourless bottles of 125 mL with grey plastic stoppers packed in a carton containing 5 or 10 bottles.
ULTRAVIST 370: Colourless pre-filled plastic cartridges of 100 and 125 mL packed into a carton containing 1x 5 cartridges or 2 x 5 cartridges.
ULTRAVIST 370: Colourless bottles of 200 mL with grey plastic stoppers packed in a carton containing 1 or 10 bottles.
ULTRAVIST 370: Colourless bottles of 500 mL with grey plastic stoppers packed in a carton containing 1 or 8 bottles.

6.6 Special precautions for disposal of a used medicine or waste derived from such medicine and other handling of the product.

Instructions for use/handling

ULTRAVIST should be warmed to body temperature prior to use.

Inspection
ULTRAVIST is supplied ready to use as a clear, colourless to pale yellow solution.
ULTRAVIST should be visually inspected prior to use and must not be used, if discoloured, nor in the presence of particulate matter (including crystals) or if containers are defective. As ULTRAVIST is a highly concentrated solution, crystallisation (milky-cloudy appearance and/or sediment at the bottom, or floating crystals) may occur very rarely.

Vials
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 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 medium solution not used in one examination for a given patient is to be discarded.

Large volume containers (only for intravascular administration)
The following applies to the multiple withdrawal of contrast medium from containers of 200 mL or more.

The multiple withdrawal of contrast medium must be done utilising a device approved for multiple use.

The rubber stopper of the bottle should never be pierced more than once to prevent large amounts of microparticles from the stopper getting into the solution.
The contrast medium must be administered by means of an automatic injector, or by other approved

procedures which ensure sterility of the contrast medium.
The tube from the injector to the patient (patient's tube) must be replaced after every patient to avoid cross contamination.

The connecting tubes and all disposable parts of the injector system must be discarded when the infusion bottle is empty or ten hours after first opening the container.
Instructions of the device manufacturer must be followed.
Unused ULTRAVIST in opened containers must be discarded ten hours after first opening the container.
Prefilled plastic cartridges
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.
Instructions of the device manufacturer must be followed.
Any contrast medium solution not used in one examination must be discarded.

7. NAME AND BUSINESS ADDRESS OF THE APPLICANT

Bayer (Pty) Ltd
27 Wrench Road,
Isando,
1609
Telephone: 011 921 5911

8. REGISTRATION NUMBER

ULTRAVIST 300 20 mL vial:	V/28/175
ULTRAVIST 300 50 mL bottle:	V/28/176
ULTRAVIST 300 75 mL bottle and pre-filled plastic cartridge:	28/28/0642
ULTRAVIST 300 100 mL bottle and pre-filled plastic cartridge:	V/28/177
ULTRAVIST 300 125 mL bottle and pre-filled plastic cartridge:	46/28/0109
ULTRAVIST 300 200 mL bottle:	33/28/0082
ULTRAVIST 300 500 mL bottle:	33/28/0083
ULTRAVIST 370 50 mL bottle:	V/28/178
ULTRAVIST 370 100 mL bottle and pre-filled plastic cartridge:	V/28/179
ULTRAVIST 370 125 mL bottle and pre-filled plastic cartridge:	46/28/0110
ULTRAVIST 370 200 mL bottle:	28/28/0643
ULTRAVIST 370 500 mL bottle:	33/28/0084

9. DATE OF FIRST AUTHORISATION

29 September 1989

10. DATE OF REVISION OF TEXT
13 March 2026