1. NAME OF THE MEDICINAL PRODUCT
Ultravist 300/370, solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ultravist 300: 1ml contains 623 mg iopromide (equivalent to 300 mg iodine)
Ultravist 370: 1ml contains 769 mg iopromide (equivalent to 370 mg iodine)

Excipient: Each ml contains up to 0.01109 mmol (equivalent to 0.2549 mg) of sodium (see Appendix 1)

For a full list of excipients, see section 'List of excipients'

3. PHARMACEUTICAL FORM
Solution for injection/infusion
Clear, very slightly brown, very slightly brownish-yellow or very slightly yellow solution.
The physico-chemical properties of Ultravist at the concentrations listed below are:

Iodine concentration (mg/ml)	300	370
Osmolality (osm/kg H_2O) at 37 °C	0.59	0.77
Viscosity (mPa·s)		
at 20 °C	8.9	22.0
at 37 °C	4.7	10.0
Density (g/ml)		
at 20 °C	1.328	1.409
at 37 °C	1.322	1.399
pH-value	6.5-8.0	6.5-8.0

4. CLINICAL PARTICULARS
4.1 Indication (s)
This medicinal product is for diagnostic use only.

Ultravist 300:
Contrast enhancement in computerized tomography (CT), digital subtraction angiography (DSA), intravenous urography, phlebography of the extremities, venography, arteriography, visualization of body cavities (e.g. arthrography, hysterosalpingography, fistulography) **with the exception of myelography, ventriculography, cisternography.**

Ultravist 370:
Contrast enhancement in computerized tomography (CT), digital subtraction angiography (DSA), intravenous urography, arteriography and especially angiocardiography, visualization of body cavities (e.g. arthrography, fistulography) **with the exception of myelography, ventriculography, cisternography.**

4.2 Dosage and method of administration

4.2.1 General information

- Dietary suggestions

Normal diet may be maintained up to two hours prior to the examination. During the last two hours the patient should refrain from eating.

- Warming prior to use

Contrast media which are warmed to body temperature before administration are better tolerated and can be injected more easily because of reduced viscosity. Using an incubator, only the calculated number of bottles needed for the examination day should be warmed up to 37°C. If protected from daylight, longer periods of warming have shown no change in chemical purity. However, three months must not be exceeded.

4.2.2 Dosage regimen

4.2.2.1 Dosage for intravascular use

Intravascular administration of contrast media should, if possible, be done with the patient lying down.

In patients suffering from marked renal or cardiovascular insufficiency, and in patients in a poor general condition, the contrast medium dose must be kept as low as possible. In these patients it is advisable to monitor renal function for at least 3 days following the examination.
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 kilo (kg) body weight (BW) as indicated below.

Generally, doses of up to 1.5 g iodine per kg body weight are well tolerated. Between separate injections the body should be given enough time for the influx of interstitial fluid to normalize the increased serum osmolality. If it is necessary in particular instances to exceed a total dose of 300 to 350 ml in the adult, additional water and possibly electrolytes should be given.

Recommended doses for single injections:

Conventional angiography

Aortic arch angiography	50 - 80 ml Ultravist 300
Selective angiography	6 - 15 ml Ultravist 300
Thoracic aortography	50 - 80 ml Ultravist 300/370
Abdominal aortography	40 - 60 ml Ultravist 300
Arteriography:	
Upper extremities	8 - 12 ml Ultravist 300
Lower extremities	20 - 30 ml Ultravist 300

Angiocardiography:

Cardiac ventricles	40 - 60 ml Ultravist 370
Intracoronary	5 - 8 ml Ultravist 370

Venography:	
Upper extremities	15 - 30 ml Ultravist 300
Lower extremities	30 - 60 ml Ultravist 300

Intravenous DSA
The i.v. injection of 30 - 60 ml Ultravist 300/370 as a bolus (flow rate: 8 - 12 ml/sec. into the cubital vein; 10 - 20 ml/sec. into the vena cava) is only recommended for contrast demonstrations of great vessels of the trunc. The amount of contrast medium remaining in the veins can be reduced and diagnostically used by flushing with isotonic sodium chloride solution as a bolus immediately afterwards.

Adults:
30 - 60 ml Ultravist 300/370.

Computerized 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 but especially in multi-slice technique allows the rapid acquisition of a volume of data during single breath-hold. To optimize the effect of the i.v. administered bolus (80-150 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 CT

In computerized 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

Adults:
Ultravist 300: 1.0 - 2.0 ml/kg BW
Ultravist 370: 1.0 - 1.5 ml/kg BW

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.

Newborns (<1 month)	1.2 g I/kg BW	= 4.0 ml/kg BW Ultravist 300 = 3.2 ml/kg BW Ultravist 370
Infants	1.0 g I/kg BW	= 3.0 ml/kg BW Ultravist 300

(1 month-2 years)		= 2.7 ml/kg BW Ultravist 370
Children (2-11 years)	0.5 g I/kg BW	= 1.5 ml/kg BW Ultravist 300 = 1.4 ml/kg BW Ultravist 370
Adolescents and adults	0.3 g I/kg BW	= 1.0 ml/kg BW Ultravist 300 = 0.8 ml/kg BW 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 injected 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 - 3 minutes after administration of the contrast medium. In newborns, infants and patients with impaired renal function later films may improve visualization of the urinary tract.

4.2.3 Additional information on special populations

4.2.3.1 Newborns (< 1 month) and infants (1 month -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.

4.2.3.2 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 beside those described in subsection ‘Dosage regimen’.

4.2.3.3 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.

4.2.3.4 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 ‘Special warnings and precautions for use’ and ‘Pharmacokinetic properties’).

4.3 Contraindications
There are no absolute contraindications to the use of Ultravist.

4.4 Special warnings and special precautions for use
4.4.1 For all indications
4.4.1.1 Hypersensitivity reactions
Ultravist can be associated with anaphylactoid / hypersensitivity or other idiosyncratic reactions characterized by cardiovascular, respiratory and cutaneous manifestations.

Allergy-like reactions ranging from mild to severe reactions including shock are possible (see section '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 (see also section 'Interactions with other medicinal products and other forms of interaction').

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

4.4.1.2 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 thyreotoxic crisis in these patients. Testing of thyroid function prior to Ultravist administration and/or 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 pediatric patients. Evaluate the potential risk of hypothyroidism in patients with known or suspected thyroid diseases before use of iodinated contrast media.

In neonates, specially 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.

4.4.1.3 CNS disorders

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 a 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.

4.4.1.4 Hydration

Adequate hydration status must be assured in all patients before intravascular or intrathecal Ultravist administration in order to minimize the risk of contrast media-induced nephrotoxicity (see also subsection '4.4.2.1 Acute Kidney Injury'). 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 subsection '4.4.2.1 Acute Kidney Injury', '4.4.2.2 Cardiovascular disease', '4.8.2 Tabulated list of adverse reactions.'

4.4.1.5 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 minimize the state of anxiety in such patients.

4.4.1.6 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.

4.4.2 Intravascular use

4.4.2.1 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. Acute renal failure may occur in some cases.
Risk factors include, e.g.:
- pre-existing renal insufficiency (see subsection '4.2.3.4 Patients with renal impairment'),
- dehydration (see subsection '4.4.1.4. Hydration')
- diabetes mellitus
- multiple myeloma / paraproteinemia
- 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 $m^{2)}$ 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 m^2) are at increased risk of PC-AKI with intra-venous or intra-arterial contrast administration with second pass renal exposure (see subsection '4.4.1.4 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.

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

The intravascular injection of Ultravist may precipitate pulmonary edema in patients with heart failure.

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

4.4.2.4 Myasthenia gravis
The administration of Ultravist media may aggravate the symptoms of myasthenia gravis.

4.4.2.5 Thromboembolic events
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 catheterization 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 minimize the length

of the procedure so as to minimize the risk of procedure-related thrombosis and embolism.

4.4.3 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 anticonvulsive measures is recommended.

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

4.5 Interaction with other medicaments and other forms of interaction
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 treated with metformin may be at an increased risk of developing lactic acidosis, especially those with prior renal impairment (see section 'Special warnings and precautions for use' – subsection 'Intravascular use' – 'Acute Kidney Injury').

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 Pregnancy and lactation
4.6.1 Pregnancy
Pregnancy: Adequate and well-controlled studies in pregnant women have not been conducted. It has not been sufficiently demonstrated that non ionic contrast media are safe for use in pregnant patients. Since, wherever possible, radiation exposure should be avoided during pregnancy, the benefits of any X-ray examination, with or without contrast media, should be carefully weighed against the possible risk.

Animal studies do not indicate harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development following diagnostic application of iopromide in humans.

4.6.2 Lactation
Safety of Ultravist for nurse infants has not been investigated. Contrast media are poorly excreted in human breast milk. Harm to the nurse infant is not likely (see also section 'Special warnings and precautions for use' – subsection 'Thyroid dysfunction').

4.7 Effects on ability to drive and use machines
Not known

4.8 Undesirable effects

4.8.1 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 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.

4.8.2 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).

The adverse drug reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under ‘not known’.

System organ class	**Common**	**Uncommon**	**Rare**	**Not Known**
Immune system disorders		Hypersensitivity/Anaphylactoid reactions hypersensitivity (anaphylactoid shock[§]) *), respiratory arrest[§]) *), bronchospasm*), laryngeal*) / pharyngeal*) / face edema, tongue edema[§]), laryngeal / pharyngeal spasm[§]), asthma[§]) *), conjunctivitis[§]), lacrimation[§]), sneezing, cough, mucosal edema, rhinitis[§]), hoarseness[§]), throat		

		irritation[§]), urticarial, pruritus, angioedema)		
Endocrine disorders				Thyrotoxic crisis, Thyroid disorder
Nervous system disorders	Dizziness, Headache, Dysgeusia	Vasovagal reactions, Confusional state, Restlessness, Paraesthesia / hypoaesthesia, Somnolence		Coma*), Cerebral ischaemia / infarction*), Stroke*), Brain edema [a]) *), Convulsion*), Transient cortical blindness [a]), Loss of consciousness, Agitation, Amnesia, Tremor, Speech disorders, Paresis / paralysis
Eye disorders	Blurred / disturbed vision			
Ear and labyrinth disorders				Hearing disorders
Cardiac disorders	Chest pain/ discomfort	Arrhythmia*)	cardiac arrest, myocardial ischemia *)/ , Palpitations	Myocardial infarction*), Cardiac failure*), Bradycardia*), Tachycardia, Cyanosis*)
Vascular disorders	Hypertension Vasodilatation	Hypotension*)		Shock*), Thromboembolic events [a)] Vasospasm [a)]
Respiratory, thoracic and mediastinal disorders		Dyspnea[*)]		Pulmonary edema*), Respiratory insufficiency*), Aspiration*)
Gastrointestinal disorders	Vomiting, Nausea	Abdominal pain		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 generalized exanthematous pustulosis (AGEP),Rash, Erythema, Hyperhydrosis
Musculoskeletal, connective tissue and bone disorders				Compartment syndrome in cases of extravasation [a)]
Renal and urinary disorders				Renal impairment [a)] , Acute renal failure [a)]
General disorders and administration site conditions	Pain, Injection site reactions (various kinds, e.g. pain, warmth[§]), edema[§]), inflammation and soft tissue injury[§]) in case of extravasation), Feeling hot	Edema		Malaise, Chills, Pallor
Investigations				Body temperature fluctuation

Table 1: Adverse drug reactions (ADRs) reported in clinical trials or during post-marketing surveillance in patients treated with Ultravist

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

[a] intravascular use only

[§]) identified only during post-marketing surveillance (frequency not known)

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.

In addition to the ADRs listed above, the following ADRs have been reported with 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.

4.8.3 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

Skin and subcutaneous Tissue Disorders
Severe cutaneous adverse reactions [e.g. Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)] have been reported in post-marketing experience of iodinated contrast media.

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

4.9.1 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 ‘Pharmacokinetic properties’).

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Watersoluble, nephrotropic, low osmolar X-ray contrast media
ATC code: V08AB05

The contrast-giving substance in the Ultravist formulations 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.

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

5.2 Pharmacokinetic properties
5.2.1 General information

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

5.2.2 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 ($\leqslant$ 0.3% of the dose were found in rabbit fetuses). 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 were about factor 40 lower compared to maximum serum levels reached after respective intravenous doses.

5.2.3 Metabolism
Iopromide is not metabolized.

5.2.4 Elimination
The terminal elimination half-life 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 fecal route within 3 days.

Approximately 60% of the dose are excreted within 3 hours after intravenous administration via urine. In the mean $\geqslant$ 93% of dose were 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 80% 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.

5.2.5 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}, $t_{1/2}$)

5.2.6 Characteristics in special patient populations
5.2.6.1 Elderly population (aged 65 years and above)
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 h in young healthy volunteers, terminal half-lives are similar. The minor differences correspond to the physiologically reduced glomerular filtration rate with age.

5.2.6.2 Pediatric population
Pharmacokinetics of iopromide have not been investigated in the pediatric population (see section 'Dosage and method of administration').

5.2.6.3 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> CLCR >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 (CLCR = 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 ⩾ CLCR > 30 ml/min/1.73 m^2) and 11.6 hours (CV = 49%) in severely impaired patients not depending on dialysis (CLCR = 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 mildly to moderately and 51% in severely impaired compared to more than 95% in healthy volunteers.

5.2.6.4 Patients with hepatic impairment
Elimination is not affected by impaired liver function because iopromide is not metabolized and only about 2 % of dose are excreted in feces.

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.

5.3.1 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.

5.3.2 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.

5.3.3 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 disodium edetate
hydrochloric acid (for pH adjustment)
sodium hydroxide (for pH adjustment)
tromethamine
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

Please refer to labels.
Ten hours after first opening the container (ampoule, vial, bottle).

6.4 Special precautions for storage

Protect from light and ionizing radiation. Do not store above 30°C.
Store all drugs properly and keep them out of reach of children.

6.5 Nature and contents of container

Ultravist 300:

- Vials of 20 and 30 ml
- Bottles of 50, 75,100, 125, 150, 200 and 500 ml

Ultravist 370:

- Vials of 20 and 30 ml
- Bottles of 50, 75, 100, 125, 150, 200, 250 and 500 ml

6.6 Instructions for use/handling

Ultravist should be warmed to body temperature prior to use.

6.6.1 Visual inspection

Contrast media should be visually inspected prior to use and must not be used, if discolored, nor in the presence of particulate matter (including crystals) or defective containers. As Ultravist is a highly concentrated solution, crystallization (milky-

cloudy appearance and/or sediment at bottom, or floating crystals) may occur very rarely.

6.6.2 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 max. 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 solution not used in one examination for a given patient is to be discarded.

6.6.3 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 utilizing 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.

7. APPENDICES
7.1 Appendix 1
7.1.1 Excipients
This medicinal product 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’

Manufactured by:
Bayer AG
Müllerstraße 178
13353 Berlin
Germany

Date of last revision
16 January 2023