

Data Sheet

ULTRAVIST®

Solution for Infusion

Iopromide 499 mg/mL, 623 mg/mL and 769 mg/mL

Name of the Medicine

Proprietary Name

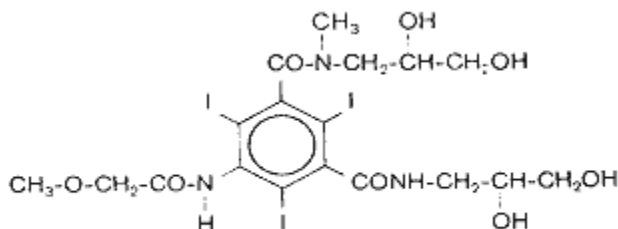
ULTRAVIST 240, ULTRAVIST 300, ULTRAVIST 370

Non-proprietary Name

Iopromide

ULTRAVIST is a non-ionic contrast medium containing iopromide as the active ingredient.

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

Chemical Formula: C₁₈H₂₄I₃N₃O₈

Description

Iopromide is a triiodinated, non-ionic, water-soluble X-ray contrast medium.

ULTRAVIST Injection 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. ULTRAVIST also contains small amounts of trometamol, sodium calcium edetate and dilute hydrochloric acid (10%) in water for injections.

ULTRAVIST is available in 3 strengths. Iodine and iopromide content of each strength is as given below:

ULTRAVIST 240: Each mL of injection contains 240 mg iodine and 499 mg iopromide, with bottles of 10 mL and 50 mL having iodine contents of 2.4 g and 12 g respectively, and having iopromide contents of 5.0 g and 24.9 g respectively.

ULTRAVIST 300: Each mL of injection contains 300 mg iodine and 623 mg iopromide, with bottles of 20 mL, 50 mL, 75 mL and 100 mL having iodine contents of 6 g, 15 g, 22.5 g and 30 g respectively, and having iopromide contents of 12.5 g, 31.2 g, 46.7 g and 62.3 g, respectively.

ULTRAVIST 370: Each mL of injection contains 370 mg iodine and 769 mg iopromide, with bottles of 30 mL, 50 mL, 75 mL, 100 mL, and 200 mL having iodine contents of 11.1 g, 18.5 g, 27.8 g, 37.0 g and 74.0 g respectively, and having iopromide contents of 23.1 g, 38.4 g, 57.7 g, 76.9 g, and 153.8 g respectively.

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
<i>Viscosity (mPa.s or cP)</i>			
at 20°C	4.9	8.9	22.0
at 37°C	2.8	4.7	10.0
<i>Osmolality at 37°C</i>			
(osm/kg H ₂ O)	0.48	0.59	0.77
<i>Osmolality at 37°C</i>			
(osm/L solution)	0.36	0.43	0.49
<i>Osmotic Pressure</i>			
Density (g/mL) 20°C	1.262	1.330	1.409

Property	ULTRAVIST 240 240 mg I/mL	ULTRAVIST 300 300 mg I/mL	ULTRAVIST 370 370 mg I/mL
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).

Pharmacology

Pharmacodynamic Properties

Iopromide, which is the contrast-giving substance in the ULTRAVIST formulation, is a derivative of triiodinated isophthalic acid in which the firmly bound iodine absorbs the X-rays.

Pharmacokinetics

Distribution

Following intravascular administration, ULTRAVIST is very rapidly distributed in the extracellular space, the half-life being 3 minutes.

Plasma protein binding with a concentration of 1.2mg I /mL is $0.9 \pm 0.2\%$. It is unable to cross the intact blood-brain barrier but a small amount does cross the placental barrier (rabbit).

Five minutes after an intravenous bolus injection of ULTRAVIST 300, $28 \pm 6\%$ of the dose was found in the total plasma volume, irrespective of the size of the dose. Following intrathecal administration, maximum iodine concentrations of 4.5 % of the administered dose per total plasma volume were observed after 3.8 hours.

Metabolism

No metabolites were detected in man following the administration of the clinically relevant doses of ULTRAVIST.

Elimination

The elimination half-life in patients with normal kidney function is approximately 2 hours, irrespective of the dose. Under the doses recommended for diagnostic purposes, filtration of ULTRAVIST is exclusively glomerular. Renal excretion is approximately 18 % of the dose within 30 minutes p. inj., approximately 60 %

within 3 hours p. inj. and 92 % within 24 hours p. inj. The total clearance was 110 and 103 mL/min. at the lower (150 mg I/mL) and at the higher dose (370 mg I/mL) levels, respectively.

After lumbar myelography, ULTRAVIST is almost completely excreted renally within 72 hours with a prolonged half-life. Major deviations of the plasma half-life have been observed.

Characteristics in patients

In end stage renal failure patients, non-ionic contrast media can be eliminated by dialysis.

Elimination in patients with impaired liver function is not affected because only 1.5 % of the dose is excreted in faeces after 3 days.

Indications

For diagnostic use.

ULTRAVIST 240/300/370

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 angiocardiology.

ULTRAVIST 300/370: Not for intrathecal use.

Contraindications

ULTRAVIST (iopromide) should not be administered to patients with known hypersensitivity or previous reaction to iodinated contrast media or any excipients.

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

Hysterosalpingography must not be performed during pregnancy or in the presence of acute inflammatory processes in the pelvic cavity.

Precautions

For All Indications

The following warnings and precautions apply to any mode of administration, however, the risks mentioned are higher in intravascular administration. THIS MEDICATION SHOULD USUALLY NOT BE USED WHEN THE FOLLOWING MEDICAL PROBLEM EXISTS

Hypersensitivity Reactions

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.

Patients with hypersensitivity or a previous reaction to iodinated contrast media are at increased risk of having a severe reaction. However, such reactions are irregular and unpredictable in nature.

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 Adverse Effects). Most of these reactions occur within one hour 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

Patients who experience such reactions while taking beta blockers may be resistant to treatment effects of beta agonists (see also Interactions with Other Medicines).

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. If premedication is given, a corticosteroid regimen is recommended.

If hypersensitivity reactions occur (see Adverse Effects), administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via a venous access. It is therefore advisable to use a flexible indwelling cannula for intravenous contrast medium administration. To permit immediate countermeasures to be taken in emergencies, appropriate medicines, an endotracheal tube and a respirator should be ready at hand.

Risk-benefit should be considered when the following medical problems exist (including general precautions on hypersensitivity)

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

Congestive Heart Failure

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.

Impaired Renal Function

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.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinaceous diseases, who are prone to disease-induced renal insufficiency and/or failure. Although neither the contrast agent nor dehydration has proven to be the cause of the renal insufficiency (or worsening renal insufficiency) in myelomatous patients, it has been speculated that the combination of both may be causative. Special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Pheochromocytoma

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.

Paediatrics

Paediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, a sensitivity to medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dL. The injection rates in small vascular beds, and the relationship of the dose by volume or concentration in small paediatric patients have not been established. Caution should be exercised in selecting the dose.

The Elderly

Underlying vascular pathology and neurological disorders often seen in the elderly constitute an increased risk of adverse reactions to iodinated contrast media.

Very Poor State of Health

The need for examination merits particularly careful consideration in patients with a very poor general state of health.

Carcinogenicity, Mutagenicity and Impairment of 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).

Use in Pregnancy

Category B2

Embryotoxicity including teratogenicity studies have been performed in rats and rabbits at doses up to 3.7g I/kg BW. These studies did not indicate an increased risk of adverse effects to the foetus following the intended diagnostic use in humans.

There are, however, no adequate and well-controlled studies in pregnant women.

Therefore, 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 nursing infants has not been investigated. Contrast media are poorly excreted in human breast milk. From experience gained so far, no harm to the nursing infant is likely to occur.

Intravascular Use

Renal Impairment

Contrast media-induced nephrotoxicity, presenting as a transient impairment of renal function, may occur after intravascular administration of ULTRAVIST. Acute renal failure may occur in rare cases.

Risk factors include, for example,

- pre-existing renal insufficiency
- dehydration
- diabetes mellitus
- multiple myeloma / paraproteinemia
- repetitive and/or large doses of ULTRAVIST

Adequate hydration should be ensured in all patients who receive ULTRAVIST administration 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.

Avoiding additional strain on the kidneys in the form of nephrotoxic medicines, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, major surgery etc. until the contrast medium has been cleared.

Postponing a new contrast medium examination is recommended until renal function returns to pre-examination levels.

Patients on dialysis may receive contrast media for radiological procedures as iodinated contrast media are cleared by the dialysis process.

In patients with severely restricted renal function, 24 hours are recommended to elapse between two iodinated contrast medium examination sessions.

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.

If clinically indicated, haemodialysis is an effective method for eliminating iodinated contrast medium from the body. Correlating the time of the contrast medium to the dialysis schedule is unnecessary. The patient should not be re-exposed to contrast media before the kidney function has returned to its previous function. If contrast medium is to be given again, the patient must be adequately hydrated.

Cardiovascular Disease

There is increased risk of clinically relevant haemodynamic changes and arrhythmia in patients with significant cardiac disease or severe coronary artery disease.

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 preexisting cardiac disease.

The intravascular injection of contrast media may precipitate pulmonary oedema in patients with heart failure.

CNS Disorders

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

Patients with Autoimmune Disorders

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

Myasthenia Gravis

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

Alcoholism

Acute or chronic alcoholism may increase blood-brain barrier permeability. This facilitates the passage of the contrast medium into cerebral tissue, possibly

leading to CNS reactions. Caution must also be exercised in alcoholics and drug addicts because of the possibility of a reduced seizure threshold.

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.

The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

Caution is advised in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

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 this therapy when receiving the contrast medium intrathecally.

Caution must be exercised in alcoholics and drug addicts because of the possibility of a reduced seizure threshold.

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.

Interactions with Other Medicines

Biguanides (metformin)

Transient renal impairment associated with the use of ULTRAVIST can lead to biguanide accumulation and the development of lactic acidosis in patients who are taking biguanides. As a precaution, biguanides should be stopped 48 hours before until at least 48 hours after contrast medium administration and reinstated only after baseline renal function has been regained.

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 (also see Precautions).

Interleukin-2

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

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.

Effects on Ability to Drive and Use Machines

As with all iodinated contrast media, there is a possibility of delayed reactions following intravascular administration in rare cases.

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.

Adverse Effects

In order to give an approximate indication of incidence the following definitions apply when the words "common", "uncommon" and "rare" appear in the text:

- common: incidence > 1: 100
- uncommon: incidence < 1: 100, but > 1: 1000
- rare: incidence < 1: 1000

Intravascular Use

Side effects in association with the use of iodinated intravascular contrast media are usually mild to moderate and transient in nature. However, severe and life-threatening reactions as well as deaths have been reported.

Nausea, vomiting, a sensation of pain and a general feeling of warmth are the most frequently recorded reactions.

Anaphylactoid reactions/hypersensitivity

Mild angioedema, conjunctivitis, coughing, pruritus, rhinitis, sneezing and urticaria have been reported commonly. These reactions, which can occur irrespective of the amount administered and the mode of administration, may be the first signs of incipient state of shock. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via a venous access (see Precautions).

Severe reactions requiring emergency treatment can occur in the form of a circulatory reaction accompanied by peripheral vasodilatation and subsequent hypotension, reflex tachycardia, dyspnoea, agitation, confusion and cyanosis possibly leading to unconsciousness.

Bronchospasm, laryngeal spasm or oedema and hypotension may occur in rare cases.

Delayed contrast medium reactions are rare (see Precautions).

Body as a whole

Heat sensations and headache have been reported as being common. Malaise, chills or sweating and vasovagal reactions are uncommon.

In rare cases alterations in body temperature and swelling of salivary glands are possible.

Respiratory

Transient disturbance in respiratory rate, dyspnoea and respiratory distress and coughing are common.

Respiratory arrest and pulmonary oedema are rare reactions.

Cardiovascular

Clinically relevant transient disturbance in heart rate, blood pressure, disturbance in cardiac rhythm or function and cardiac arrest are rare.

Severe reactions requiring emergency treatment are rare and can occur in the form of a circulatory reaction accompanied by peripheral vasodilatation and subsequent hypotension, reflex tachycardia, dyspnoea, agitation, confusion and cyanosis possibly leading to unconsciousness.

Serious thromboembolic events causing myocardial infarction have been reported in rare cases.

Gastrointestinal

Nausea and vomiting are common reactions. Taste disturbance is uncommon. Abdominal pain has been reported as being rare.

Cerebrovascular

Cerebral angiography and other procedures in which the contrast medium reaches the brain in high concentrations with the arterial blood can be accompanied by transient neurological complications such as: dizziness and headache uncommonly, agitation or confusion, amnesia, disturbed speech, vision, hearing, convulsions, tremor, paresis/paralysis, photophobia, temporary blindness, coma, somnolence (rare).

Serious, in isolated cases fatal, thromboembolic events causing stroke have been reported on rare occasions.

Renal

In rare cases renal impairment or acute renal failure have been reported.

Skin

Mild angioedema, flush reaction with vasodilatation, urticaria, pruritus and erythema have been commonly observed.

Toxic skin reactions such as the mucocutaneous syndrome (e.g. Stevens-Johnson's or Lyell syndrome) may develop in rare cases.

Local irritation (injection site)

Local pain occurs mainly in peripheral angiography. Extravasation of contrast media, including Ultravist, gives rise to local pain, and oedema, but usually recedes without sequela. However, inflammation and even tissue necrosis have been seen on very rare occasions. Thrombophlebitis and venous thrombosis are rare.

Intrathecal Use

Because of the route of administration the majority of the reactions after myelography occur some hours after the administration, due to the slow absorption from the area of administration and distribution in the whole organism primarily through diffusion controlled processes.

Based on the experience with other non ionic contrast media, the following side effects may occur after the administration of Ultravist 240:

Anaphylactoid reactions/hypersensitivity

Anaphylactoid reactions with circulatory disturbance such as severe blood pressure drop leading to loss of consciousness or cardiac arrest and life threatening shock are rare, but fatalities have been reported.

Hypersensitivity reactions like urticaria, cutaneous angioedema, other skin reactions, dyspnoea or respiratory distress in the form of bronchospasm, or laryngeal oedema are rare. Please refer to the corresponding section on intravascular use for a full text on anaphylactoid reactions.

Central nervous system (CNS)

Headache, nausea, neck stiffness and vomiting have been observed commonly. Severe headaches lasting several days may occur. These reactions may largely be attributed to pressure loss in the subarachnoid space resulting from the lumbar puncture. Therefore, an effort should be made to remove only as much fluid as is being replaced by the contrast medium. A volume of contrast medium in excess of the fluid removed does not lead to a pressure increase in the subarachnoid space.

Meningeal irritation giving rise to photophobia and meningism is common. Pleocytosis or frank meningitis do occur rarely. Also in rare cases, aseptic or chemical meningitis have been reported, however cases of meningitis should be regarded as being bacterial unless this can be positively ruled out.

The following mostly transient side effects may occur rarely: agitation, amnesia, asthenia, cortical blindness, deafness, disturbance of motor functions (e.g. speech or movement), dizziness, hallucinations, paresis/paralysis, psychotic behaviour, convulsions, syncope, tinnitus and nystagmus, tremor, visual disturbances, clinically relevant minor EEG-changes.

Body as a whole

Alterations in body temperature, chills or sweating and malaise are rare.

Respiratory

In rare cases dyspnoea, respiratory distress and transient disturbance in respiratory rate have been reported.

Cardiovascular

Clinically relevant disturbance in cardiac rhythm or function and transient disturbance in heart rate and/or blood pressure may rarely occur.

Skin

Angioedema and urticaria have been reported as being rare.

Local irritation (injection site)

Mild local pain, paraesthesia, and radicular pain is common.

In clinical trials with a relatively small number of cases, the following side effects have been observed with Ultravist 240 up to now, however, for the general use of Ultravist 240 the other above-mentioned side effects cannot be excluded: headache, nausea, vomiting, back pain, neck stiffness, neuralgia, pain in extremities, injection site pain, dizziness, hypotension, deafness, myasthenia, neuropathy, tinnitus, and rash.

Dosage and Administration

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.

Hydration

Adequate hydration must be assured before and after intravascular and intrathecal contrast medium administration. This applies especially to patients with multiple myeloma, diabetes mellitus, polyuria, oliguria, hyperuricaemia, as well as to newborns, infants, small children and elderly patients.

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.

Newborns (< 1 month) and infants (1 month - 2 years)

Young infants (age < 1 year) and especially newborns 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.

Anxiety

Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium - related reactions. These patients may be given a sedative.

Visual Inspection

Contrast media such as ULTRAVIST should be visually inspected prior to use and must not be used in the presence of particulate matter (including crystals) or if the solution is discoloured or the container 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 such as ULTRAVIST may be tolerated better if it is warmed to body temperature before administration 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 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.

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 Administration

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be observed for at least 30 minutes, since the majority of reactions occur within this time.

The dosage should be adapted to age, weight, cardiac output and general condition of the patient. Also on the clinical question and 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 kilogram (kg) body weight (BW) as indicated below.

Generally, doses of up to 1.5g iodine per kg body weight are well tolerated (corresponding to 3 - 5 mL ULTRAVIST 300/kg body weight).

Between separate injections the body should be given enough time for the influx of interstitial fluid to normalise the increased serum osmolality. If it is necessary to exceed a total dose of 300 to 350 mL in the adult, additional water and possibly electrolytes should be given.

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.

Recommended doses for single injections:

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 body weight	5.0 mL/ kg BW ULTRAVIST
		240
		4.0 mL/ kg BW ULTRAVIST
		300
Infants (1 month - 2 years)	1.0 g I/kg body weight	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
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

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 (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.

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

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 BW

ULTRAVIST 300: 1.0 - 2.0 mL/kg BW

ULTRAVIST 370: 1.0 - 1.5 mL/kg BW

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 should be adapted to age, weight, cardiac output and general condition of the patient, the clinical question, examination technique and the nature and volume of the vascular region to be investigated.

Aortic arch angiography	50 - 80mL ULTRAVIST 300
Retrograde carotid angiography	30 - 40 mL ULTRAVIST 300
Selective angiography	6 - 15mL ULTRAVIST 300
Thoracic aortography	50 - 80mL ULTRAVIST 300 or 370
Abdominal aortography	40 - 60mL ULTRAVIST 300

Arteriography:

Upper extremities	8 - 12mL ULTRAVIST 300
Lower extremities	20 - 30mL ULTRAVIST 300

Angiocardiography:

Cardiac ventricles	40 - 60 mL ULTRAVIST 370
Intracoronary	5 - 8 mL ULTRAVIST 370

Venography:

Upper extremities	50 - 60 mL ULTRAVIST 240
or	15 - 30 mL ULTRAVIST 300

Lower extremities 50 - 80mL ULTRAVIST 240
or 30 - 60 mL ULTRAVIST 300

Paediatric Angiocardiography

ULTRAVIST 370 mg I/mL 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.

Digital Subtraction Angiography (DSA)

Intravenous DSA

The i.v. injection of 30 - 60mL 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 injecting 20 to 40 mL isotonic sodium chloride solution as a bolus immediately afterwards.

Adults: 30 - 60 mL ULTRAVIST 300/370

Intra-arterial 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.

Intrathecal Use

Adults

The dosage may vary depending on the clinical problem, examination technique and the region to be investigated. Generally, a dose of 3 g iodine should not be exceeded in one examination.

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.

Recommended dose for single examinations:

Myelography

ULTRAVIST 240: Up to 12.5 mL for myelography

Generally, a dose of 3 g iodine should not be exceeded for one examination.

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.

Other Body Cavities

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

Recommended Doses for Single Examinations

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.

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.

Monitor fluids, electrolytes and renal function. Treatment of overdose should be directed toward the support of vital functions.

ULTRAVIST is dialysable. In the event of accidental intravascular overdose in humans, the water and electrolyte losses must be compensated by infusion. Renal function needs monitoring for at least the next 3 days. If needed, haemodialysis can be used to eliminate the bulk of the contrast medium from the patient's system.

Intrathecal Overdose

Serious neurological complications may occur. Close monitoring is recommended.

In case of an accidental intrathecal overdose, the patient must be closely monitored for signs of serious CNS disturbance over the first 12 hours. Signs may be ascending hyperreflexia or tonic-clonic spasms, in severe cases central involvement with generalized seizures, hyperthermia, stupor and respiratory depression. In order to prevent large amounts of ULTRAVIST from getting into the cisterns, aspiration of the contrast medium should be done as entirely as possible.

Presentations and Storage Conditions

ULTRAVIST 240: ULTRAVIST 300: ULTRAVIST 370:

Bottles of 10mL	Bottles of 20mL	Bottles of 30mL
Bottles of 50mL	Bottles of 50mL	Bottles of 50mL
	Bottles of 75mL	Bottles of 75mL
	Bottles of 100mL	Bottles of 100mL
		Bottles of 200mL

Not all presentations are marketed.

Store below 30°C.

Protect from light and secondary X-rays.

Instructions for Use/Handling

Contrast media must not be mixed with any other medicines to avoid the risk of possible incompatibilities.

ULTRAVIST should be warmed to body temperature prior to use.

Inspection

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

Single Dose Vials/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. Nococe - Admix cannulas, are particularly suitable).

Any contrast solution not used in one examination for a given patient is to be discarded.

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

Medicine Classification

General Sales Medicine

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