1. NAME OF THE MEDICINAL PRODUCT

Ultravist 300
Ultravist 370

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).

For the full list of excipients, see section 6.1.

The physical and chemical properties of the Ultravist solutions for injection at the concentrations indicated below are as follows:

	Ultravist 300	**Ultravist 370**
Iodine content (mg/mL)	300	370
Iodine content (g) per:		
10 mL vial	3.0	-
20 mL vial	6.0	-
50 mL bottle	15.0	18.5
100 mL bottle	30.0	37.0
150 mL bottle	45.0	55.5
200 mL bottle	60.0	74.0
500 mL bottle	150.0	185.0
Contrast medium content (mg/mL)	623	769
Contrast medium content (g) per:		
10mL vial	6.2	-
20mL vial	12.5	-
50mL bottle	31.2	38.4
100mL bottle	62.3	76.9
150mL bottle	93.5	115.3
200mL bottle	124.7	153.8
500mL bottle	311.7	384.4
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	6.5-8.0	6.5-8.0

3. PHARMACEUTICAL FORM

Solution for injection and infusion.

Clear, free of particles solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Ultravist 300:
Contrast enhancement in computerized tomography (CT), digital subtraction angiography (DSA), intravenous urography, arteriography, phlebography of the extremities, venography, 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 Posology and method of administration

- **General information**

Experience shows that contrast medium is tolerated better if it is warmed to body temperature.

Intravenous urography

Adults: The minimum dose is 0.8ml/kg body weight Ultravist 370, (1ml/kg Ultravist 300). These doses should provide adequate filling of the ureters. It may be necessary to increase the dose in individual cases.

Children: The poor concentrating ability of the immature nephron of infantile kidneys necessitates the use of relatively high doses of contrast medium, i.e. for Ultravist 300:

Neonates:	4.0 ml/kg body weight
Babies:	3.0 ml/kg body weight
Small children:	1.5 ml/kg body weight

Computerised tomography

Cranial CT: The following dosages are recommended for cranial CT:

Ultravist 300:	1-2ml/kg body weight
Ultravist 370:	1-1.5ml/kg body weight

Whole-body CT: For whole-body computerised tomography, the 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.

Angiography: The dosage depends on the age, weight, cardiac output and general condition of the patient, the clinical problem, examination technique and the nature and volume of the vascular region to be investigated.

The following dosages may serve as a guide:

Cerebral angiography	
Aortic arch angiography	50-80 ml Ultravist 300/inj.
Selective angiography	6-15 ml Ultravist 300/inj.
Thoracic aortography:	50-80 ml Ultravist 300/inj.
Abdominal aortography:	40-60 ml Ultravist 300/inj.
Peripheral angiography:	
Upper extremities:	
Arteriography	8-12 ml Ultravist 300/inj.
Venography	15-30 ml Ultravist 300/inj.
Lower extremities:	
Arteriography	20-30 ml Ultravist 300/inj.
Venography	30-60 ml Ultravist 300/inj.
Angiocardiography:	
Cardiac-ventriculography	40-60 ml Ultravist 370/inj.
Coronary angiography:	5-8 ml Ultravist 370/inj.

Digital subtraction angiography (DSA): I.V. injection of 30-60 ml Ultravist 300 or 370 as a bolus (flow-rate: 8-12 ml/second into the cubital vein; 10-20 ml/second into the vena cava) is recommended for high-contrast demonstrations of the great vessels, of the pulmonary arteries and of the arteries of the neck, head, kidneys and extremities.
Intra-arterial digital subtraction angiography requires smaller volumes and lower iodine concentrations than the intravenous technique.

Additional information on special populations

- Paediatric population

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 (see section 5.2).

- 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 renal impairment in patients with pre-existing renal impairment, the minimum possible dose should be used in these patients (see also sections 4.4, 5.1 and 5.2).

- Patients with hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment (see section 5.2).

- Elderly

When administered to elderly patients, the possibility of reduced renal function (leading to reduced clearance) should be considered (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

4.4.1 For all indications

4.4.1.1 Hypersensitivity reactions

Ultravist may be associated with anaphylactoid/hypersensitivity reactions or other idiosyncratic reactions characterised by cardiovascular, respiratory and cutaneous events.

Allergic-type undesirable effects are possible, ranging from mild to severe reactions including shock (see section “Undesirable effects”). Most of these undesirable effects occur within 30 minutes of administration. However, delayed reactions (after several hours or even several days) may also occur.

The risk of hypersensitivity reactions is higher in the following cases:
- if the patient has had a previous reaction to a contrast medium
- if the patient has a history of bronchial asthma or other allergic disorders.

Due to an increased risk of hypersensitivity reactions (including serious reactions), a particularly careful risk/benefit assessment is necessary in patients with known hypersensitivity to Ultravist or to any of the excipients of Ultravist, and in patients who have experienced a previous hypersensitivity reaction to another iodinated contrast medium.

However, these undesirable effects are sporadic and unpredictable.

Patients who experience such reactions while taking beta blockers may not respond to beta agonist treatment (see also section “Interaction 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 complications.

Due to the possibility of severe hypersensitivity reactions after administration, the patient should continue to be monitored after the procedure.

For all patients, healthcare professionals must be ready to institute emergency measures.

Premedication with corticosteroids may be considered in patients with an increased risk of allergic-type reactions and patients who have previously developed a moderate or severe acute reaction, asthma or allergy requiring medical treatment.

4.4.1.2 Severe skin reactions

Severe skin reactions, particularly cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and acute generalised exanthematous pustulosis (AGEP) that may be life-threatening or fatal have been associated with iopromide administration at a frequency that is not known.

Patients must be informed of the associated signs and symptoms and close monitoring for the onset of skin reactions is required.

In children, the skin rash observed initially may be misinterpreted as an infection, and physicians should consider the possibility of a reaction to iopromide in children who develop signs of skin rash and fever.

In most cases, these reactions occurred within 8 weeks (1 to 12 days for AGEP, 2 to 8 weeks for DRESS syndrome, and 5 days to 8 weeks for SJS/TEN).

If the patient develops a serious reaction such as SJS, TEN, AGEP or DRESS syndrome during iopromide use, iopromide must never be readministered.

4.4.1.3 Thyroid dysfunction

In patients with known or suspected hypothyroidism or goitre, a very careful risk/benefit assessment is necessary because the iodinated contrast medium may cause hyperthyroidism and a thyrotoxic crisis in these patients. In patients with known or suspected hyperthyroidism, testing of thyroid function and/or a prophylactic thyrostatic medicinal product should be considered before Ultravist administration.

Thyroid function tests indicating hypothyroidism or a transient decrease in thyroid function have been reported following administration of iodinated contrast media in adult and paediatric patients. The potential risk of hypothyroidism must be evaluated in patients with known or suspected thyroid disease prior to the use of iodinated contrast media.

Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age:
Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media (ICM) in pediatric patients 0 to 3 years of age.

The incidence has been reported between 1% and 15% depending on the age of the subjects and the dose of the iodinated contrast agent and is more commonly observed in neonates and premature infants. Neonates may also be exposed through the mother during pregnancy.
Younger age, very low birth weight, prematurity, underlying medical conditions affecting thyroid function, admission to neonatal or pediatric intensive care units, and congenital cardiac conditions are associated with an increased risk of hypothyroidism after ICM exposure.
Pediatric patients with congenital cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures.
An underactive thyroid during early life may be harmful for cognitive and neurological development and may require thyroid hormone replacement therapy.
After exposure to ICM, individualize thyroid function monitoring based on underlying risk factors, especially in term and preterm neonates.

4.4.1.4 CNS disorders

Patients with CNS disorders may be at an increased risk of neurological complications following Ultravist administration. Neurological complications are more common in the context of cerebral angiography and related procedures.

Cases of encephalopathy have been reported following the use of iopromide (see section 4.8). Contrast media-induced encephalopathy may manifest as signs and symptoms of neurological dysfunction, such as headache, vision disorders, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, loss of consciousness, coma, and cerebral oedema. Symptoms generally appear within a few minutes or hours of iopromide administration and generally resolve within a few days.

Caution should be exercised in situations in which there may be a reduced seizure threshold, as in patients with a history of epileptic episodes and in the concomitant use of specific medicinal products.

Factors which increase blood-brain barrier permeability promote the passage of the contrast medium into cerebral tissue, which may induce CNS reactions such as encephalopathy.

If contrast media-induced encephalopathy is suspected, appropriate medical care must be given and iopromide must never be readministered to this patient.

4.4.1.5 Hydration

Good hydration must be ensured in all patients before intravascular Ultravist administration (see also section "Intravascular use" – "Acute kidney injury"). This applies especially to patients presenting renal impairment risk factors, such as patients with multiple myeloma, diabetes, polyuria, oliguria or hyperuricaemia, and to newborns, babies, toddlers, young children and elderly patients.
Adequate hydration must be ensured in patients presenting renal impairment. However, the prophylactic administration of intravenous fluid in patients with moderate renal impairment (eGFR 30-59 mL/min./1.73 m^2) is not recommended as no additional benefit in terms of renal safety has been demonstrated. In patients with severe renal impairment (eGFR < 30 mL/min./1.73 m^2) and cardiac comorbidity, the prophylactic administration of intravenous fluid can lead to an increase in serious cardiac complications. See sections 4.4.2.1 *Acute kidney injury*, 4.4.2.2 *Cardiovascular disorders* and 4.8.2 *Summary table of undesirable effects*. If prophylactic intravenous fluids are administered, monitoring of cardiac function parameters is recommended.

4.4.1.6 Anxiety

Pronounced states of agitation, anxiety and pain may increase the risk of undesirable effects or intensify contrast medium-related reactions. In these patients, measures should be taken to relieve the anxiety.

4.4.1.7 Pretesting

Sensitivity testing using a small test dose of contrast medium is not recommended as it has no predictive value. Furthermore, sensitivity testing itself may lead to serious or even fatal hypersensitivity reactions.

4.4.2 Intravascular use

4.4.2.1 Acute kidney injury

Post-contrast acute kidney injury (PC-AKI) can occur after intravascular administration of Ultravist, manifesting in the form of temporary renal impairment. Acute kidney injury may also occur in a few cases.

The main risk factors are:
- pre-existing renal impairment (see section 4.2 Patients with renal impairment)
- dehydration (see section 4.4.1.5 Hydration)
- diabetes
- multiple myeloma/paraproteinaemia,
- repeated and/or high doses of Ultravist.

Patients with moderate to severe renal impairment (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) during arterial administration of contrast media with first-pass renal exposure.
Patients with severe renal impairment (eGFR < 30 mL/min./1.73 m^2) are at increased risk of PC-AKI when administration is intravenous or intraarterial with second-pass renal exposure (see section 4.4.1.5 Hydration).

Patients on dialysis and without residual renal function may receive Ultravist for radiological examinations because the iodinated contrast medium is cleared by dialysis.

4.4.2.2 Cardiovascular disease

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

Intravascular injection of Ultravist may cause pulmonary oedema in patients with heart failure.

4.4.2.3 Phaeochromocytoma

Patients with phaeochromocytoma may be at an increased risk of developing a hypertensive crisis.

4.4.2.4 Myasthenia gravis

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

4.4.2.5 Thromboembolic events

A property of non-ionic contrast media is their low interference with normal physiological functions. As a result of this, non-ionic contrast media have lower anticoagulant activity *in vitro* than ionic media. Numerous other factors not related to the contrast medium, particularly the length of examination, number of injections, catheter and syringe materials, underlying disease and concomitant medicinal products, may contribute to the development of thromboembolic events. This should therefore be borne in mind when performing vascular catheterisation procedures, and particular attention should be paid to the angiographic technique, with frequent flushing of the catheter with physiological saline (if possible with the addition of heparin) and minimisation of the length of the procedure so as to limit the risk of procedure-related thrombosis and embolism.

4.4.3 Contrast-enhanced mammography (CEM)

Contrast-enhanced mammography increases patient exposure to ionising radiation compared with standard mammography. The radiation dose depends on breast thickness, the type of mammography machine and on the system settings of the machine.
The total radiation dose for CEM remains lower than the threshold value defined in the international guidelines for mammography (below 3 mGy).

4.4.4 Information on excipients

This medicinal product contains less than 1 mmol (23 mg) sodium per 1 mL, i.e. it is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Biguanides (metformin): in patients with acute kidney injury or severe chronic kidney disease, biguanide elimination may be disrupted, leading to accumulation and the development of lactic acidosis. As the use of Ultravist may lead to renal impairment or aggravation of renal impairment, patients treated with metformin may be at an increased risk of developing lactic acidosis, especially those with pre-existing renal impairment (see section "Special warnings and precautions for use" – under 'Intravascular use' – 'Acute kidney injury'). The administration of metformin should be discontinued temporarily, at the latest from the time of administration of the iodinated contrast medium, in patients with eGFR < 30 ml/min./1.73 m^2 when administration is intravenous or intraarterial with second pass renal exposure to the iodinated contrast media, or in patients with eGFR < 45 ml/min./1.73 m^2 when administration is with first pass renal exposure. Metformin should be resumed 48 hours after administration of the contrast medium if serum creatinine/eGFR has not changed from the pre-imaging levels. If the eGFR is higher than these values, the metformin may be continued provided hydration is adequate.

Interleukin-2: previous interleukin-2 treatment (up to several weeks previously) is associated with an increase in the risk of delayed reactions to Ultravist.

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

Nephrotoxic medicines: the use of nephrotoxic medicines (for example NSAIDs, aminosides, cisplatin) should be discontinued temporarily when examining patients with eGFR < 30 ml/min./1.73 m^2 in the case of intravenous or intraarterial administration with second pass renal exposure to iodinated contrast media, or in patients with eGFR < 45 ml/min./1.73 m^2 in the case of first pass renal exposure.

4.6 Fertility, pregnancy and lactation

4.6.1 Pregnancy

No well-designed and sufficient controlled studies have been conducted in pregnant women. The safety of non-ionic contrast media in pregnant women has not been sufficiently established. Given that X-ray exposure should in any case be avoided during pregnancy whenever possible, the benefits of any radiological examination, with or without contrast media, should be carefully weighed against the possible risk.

Animal studies are inconclusive with respect to harmful effects on pregnancy, embryonic/fetal development, delivery and postnatal development following the diagnostic administration of iopromide in humans.

4.6.2 Breastfeeding

The safety of Ultravist has not been studied in breastfed infants. Contrast media are excreted only in very small amounts in breast milk. They are unlikely to harm the breastfed infant (see also section "Special warnings and precautions for use" – "Thyroid dysfunction").

4.7 Effects on ability to drive and use machines

No data available.
However, because of the risk of reactions, driving or operating machinery is not advisable for 30 minutes after the last injection (see Section 4.4).

4.8 Undesirable effects

4.8.1 Summary of the safety profile

The general safety profile of Ultravist is based on data obtained in pre-marketing studies in more than 3,900 patients and post-marketing studies in more than 74,000 patients, as well as on data from spontaneous reporting and the literature.

The most frequently reported undesirable effects (> 4%) in patients administered Ultravist are headaches, nausea and vasodilation.

The most serious undesirable effects that occur in patients administered Ultravist are as follows: anaphylactoid shock, respiratory arrest, bronchospasm, laryngeal oedema, pharyngeal oedema, asthma, coma, cerebral infarction, cerebrovascular accident, cerebral oedema, convulsions, arrhythmia, cardiac arrest, myocardial ischaemia, myocardial infarction, heart failure, bradycardia, cyanosis, hypotension, shock, dyspnoea, pulmonary oedema, respiratory failure and aspiration.

4.8.2 Summary table of undesirable effects

The undesirable effects observed with Ultravist are summarised in the table below. They are listed by System Organ Class (MedDRA version 13.0), the most appropriate MedDRA term being used to describe a specific reaction with its synonyms and related conditions.

Undesirable effects reported during clinical trials are classed according to their frequency, with frequency groups being 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 undesirable effects reported in the post-marketing period only, whose frequency could not be estimated, are listed under "unknown".

Table 1: Undesirable effects reported in clinical trials or in the post-marketing period in patients treated with Ultravist

System organ class	Common	Uncommon	Rare	Frequency unknown
Immune system disorders		Hypersensitivity/ anaphylactoid reactions (anaphylactoid shock[§)*)], respiratory arrest[§)*)], bronchospasm[*)], laryngeal[*)]/ pharyngeal[*)]/facial oedema, tongue oedema[§)], laryngeal/pharyngeal spasm[§)], asthma[§)*)], conjunctivitis[§)], lacrimation[§)], sneezing, cough, mucosal oedema, rhinitis[§)], hoarseness[§)], throat irritation[§], urticaria, pruritus, angioedema)		
Endocrine disorders				Thyrotoxic crisis, thyroid disorders
Psychiatric disorders			Anxiety	
Nervous system disorders	Dizziness, headaches, dysgeusia	Vasovagal reactions, confused state, restlessness, paraesthesia/ hypoesthesia, somnolence		Coma[*)], cerebral ischaemia/infarction[*)], cerebrovascular accident[*)], cerebral oedema[a)*)], convulsions[*)], transient loss of cortical vision[a)], loss of consciousness, agitation, amnesia, tremor, speech disorders, paresis/paralysis, contrast media-induced encephalopathy
Eye disorders	Vision disorder/ visual acuity disorder			
Ear and labyrinth disorders				Hearing disorders
Cardiac disorders	Chest pain/ discomfort	Arrythmia[*)]	Cardiac arrest[*)], myocardial ischaemia[*)], palpitations	Myocardial infarction[*)], heart failure[*)], bradycardia[*)], tachycardia, cyanosis[*)]

System organ class	Common	Uncommon	Rare	Frequency unknown
Vascular disorders	Hypertension, vasodilation	Hypotension[*)]		Shock[*)], thromboembolic events[a)], vasospasm[a)]
Respiratory, thoracic and mediastinal disorders		Dyspnoea[*)]		Pulmonary oedema[*)], respiratory failure[*)], aspiration[*)]
Gastrointestinal disorders	Vomiting, nausea	Abdominal pain		Swallowing disorders, swelling of the salivary glands, diarrhoea
Skin and subcutaneous tissue disorders				Bullous disorders (e.g. Stevens-Johnson or Lyell syndrome), rash, erythema, hyperhidrosis, acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders				Compartment syndrome in the case of extravasation[a)]
Renal and urinary disorders				Renal disorders[a)], acute kidney injury[a)]
General disorders and administration site conditions	Pain, injection site reactions (of various types such as pain, feeling of warmth[§)], oedema[§)], inflammation[§)], soft tissue lesions[§)] in the case of extravasation), hot flushes	Oedema		Feeling faint, shivering, pallor
Investigations				Fluctuation in body temperature

[*)] life-threatening and/or fatal cases have been reported
[a)] during intravascular use only
[§)] identified only during post-marketing surveillance (frequency not known)

Most reactions following use in body cavities occur a few hours after administration.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

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

4.9.1 Intravascular overdose

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

In the event of accidental intravascular overdose, it is recommended that fluids, electrolytes and renal function be monitored. Treatment of overdose should aim to support vital functions.

Ultravist is dialysable (see section 5.2 “Pharmacokinetic properties”).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: water-soluble, nephrotropic, low osmolar X-ray contrast medium.

ATC code: V08AB05

The opacifying substance in Ultravist 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 vessels or body cavities in the path of flow of the contrast agent, permitting visualisation of the internal structures until the product becomes too diluted.

Contrast-enhanced mammography (CEM)

Nine studies in a total of 1 531 patients focused on diagnostic performance in relevant fields of application.

In studies evaluating suspected breast lesions, CEM displayed a sensitivity of 96.9% to 100% and a specificity of between 69.7% and 87%, compared with digital mammography which showed a sensitivity of 96.9% and a specificity of 42.0%.

In comparative studies evaluating the precision of CEM compared with other diagnostic methods, CEM showed a difference in sensitivity and negative predictive value compared with MRI. (sensitivity 100% versus 93%; $p=0.04$ and NPV 100% versus 65%; $p<0.001$).

In addition, compared with full-field digital mammography (FFDM) combined with ultrasonography, CEM showed a sensitivity of 92.3% compared with 89.8% ($p<0.05$), a positive predictive value (PPV) of 93% compared with 88.7% ($p<0.01$) and precision of 90.2% compared with 87% ($p<0.05$).

In patients in whom MRI was contraindicated, there was a significant correlation between mammography and CEM classification and the histopathological classification. CEM showed a sensitivity of 98.8% and a specificity of 54.6% compared with 89.2% and 36.4% respectively for mammography.

In studies evaluating the presurgical assessment and staging of breast cancer, CEM showed a sensitivity, specificity, PPV, NPV and precision of 93%, 98%, 90%, 98% and 97% respectively. The surgical plan was modified by CEM in 18.4% of cases.

5.2 Pharmacokinetic properties

5.2.1 General Information

In the body, iopromide behaves like other highly hydrophilic, biologically inert, renally excreted compounds (e.g. mannitol or inulin).

5.2.2 Absorption and distribution

Following intravenous administration, plasma iopromide concentration declines rapidly due to distribution into the extracellular space and subsequent elimination. The total volume of distribution at steady-state is about 16 L, corresponding approximately to the volume of the extracellular space.

Plasma protein binding is negligible (about 1%). There is no indication that iopromide crosses the intact blood-brain barrier. A small amount crossed the placenta in animal studies (≤ 0.3% of the dose was found in rabbit fetuses). Following intrathecal administration, peak iodine concentration of approximately 4.5% of the administered dose was observed in the total plasma volume after 3.8 hours.

Following administration in the bile and/or pancreatic ducts during endoscopic retrograde cholangiopancreatography (ERCP), iodinated contrast media are systemically absorbed and reach peak plasma concentrations between 1 and 4 hours after administration. Peak serum iodine concentration, following administration of a mean dose of about 7.3 g iodine, was about 40 times lower than peak serum concentrations after administration of the respective intravenous doses.

5.2.3 Biotransformation

Iopromide is not metabolised.

5.2.4 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 is 106 ± 12 mL/min, which is comparable to renal clearance of 102 ± 15 mL/min. Iopromide is therefore almost exclusively eliminated by the kidneys. Only about 2% of the administered dose is eliminated via the faecal route within 3 days.

Approximately 60% of the dose is excreted in the urine within 3 hours of intravenous administration. On average, ≥ 93% of the dose was recovered within 12 hours. Elimination is essentially complete within 24 hours.

Following intrathecal administration for myelography of the lumbar spine, plasma elimination of iopromide takes longer, with a terminal half-life of 14.9 ± 17 hours. About 80% of iopromide is eliminated by the kidneys within 72 hours.

Following administration into the bile and/or the pancreatic ducts for ERCP, serum concentration of urinary iodine normalised within 7 days.

5.2.5 Linearity/non-linearity

The pharmacokinetic parameters of iopromide in humans are dose-dependent in some cases (e.g. C_{max}, AUC) and dose-independent in others (e.g. V_{ss}, $t_{1/2}$).

5.2.6 Characteristics in special patient populations

5.2.6.1 Elderly population (aged 65 years or more)

Middle-aged patients (49-64 years) and elderly patients (65-70 years), without severely impaired renal function, had total plasma clearance of 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 that in healthy young subjects (88 to 138 mL/min, mean 106 mL/min). Individual elimination half-lives are between 1.9 and 2.9 hours and between 1.5 and 2.7 hours respectively. Terminal half-lives are comparable to the range of 1.4 to 2.1 h in healthy young volunteers. The minor differences can be explained by glomerular filtration rate, which naturally decreases as age increases.

5.2.6.2 Paediatric Population

The pharmacokinetics of iopromide have not been studied in the paediatric population (see section “Posology 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 longer, depending on the reduced glomerular filtration rate.

Plasma clearance was reduced to 49.4 mL/min/1.73 m^2 (CV = 53%) in patients with mild or moderate renal impairment (80 > CL_{CR} > 30 mL/min/1.73 m^2) and to 18.1 mL/min/1.73 m^2 (CV = 30%) in patients with severe renal impairment not dependent on dialysis (CL_{CR} = 30-10 mL/min/1.73 m^2).

Mean terminal half-life is 6.1 hours (CV = 43%) in patients with mild to moderate renal impairment (80 ≥ CL_{CR} > 30 mL/min/1.73 m^2) and 11.6 hours (CV = 49%) in patients with severe impairment not dependent on dialysis (CL_{CR} = 30-10 mL/min/1.73 m^2).

The amount recovered in urine within 6 hours of administration was 38% in patients with mild to moderate renal impairment and 26% in patients with severe impairment, compared with more than 83% in healthy volunteers. Recovery within 24 hours of administration was 60% in patients with mild to moderate renal impairment and 51% in patients with severe renal impairment, versus more than 95% in healthy volunteers.

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

5.2.6.4 Patients with hepatic impairment

Elimination is not affected by hepatic impairment because iopromide is not metabolised and only about 2% of the dose is excreted in the faeces.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

5.3.1 Systemic toxicity

Experimental systemic tolerance studies, following repeated daily intravenous administration and repeated weekly intrathecal administration, produced no findings which oppose the use of Ultravist in humans for diagnostic purposes.

5.3.2 Genotoxicity, carcinogenic potential

In vivo and *in vitro* studies on genotoxic effects (gene, chromosomal and genome mutation tests) gave no indication of a mutagenic potential from Ultravist.

Given the absence of genotoxic effects and considering the metabolic stability, pharmacokinetics and the absence of indications of toxic effects on fast-growing tissues, as well as the fact that Ultravist is only administered once, there is no evident risk of a carcinogenic effect in humans.

5.3.3 Local tolerance and contact-sensitising potential

Local tolerance studies, following single and repeated intravenous administration and single intra-arterial, intramuscular, paravenous, intraperitoneal, intrathecal and conjunctival administration, showed that no or only negligible undesirable local effects are to be expected in human blood vessels, paravenous tissue, subarachnoid space or mucosa.

Studies on the contact-sensitising effect gave no indication of a sensitising potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injection
Hydrochloric acid 10%
Trometamol
Sodium calcium edetate
Sodium hydroxide solution, 25%

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
After opening the product is stable for 10 hours.
From a microbial point of view, the ready to use preparation should be used immediately.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Injection Vial: glass type I
Bottles: glass type II
Stopper: Chlorinated butyl rubber, 4651/40 Y11.
Flanged cap: aluminum with internal and external lacquer and colored plastic cap made of polypropylene (without product contact).

Ultravist 300
Injection vial of: 1X20 ml
Infusion Bottles of 1X50 ml, 1X75 ml, 1X200 ml, 1X500 ml, 10X100 ml.

Ultravist 370
Infusion Bottles of 1X50 ml, 1X100 ml, 1X200 ml, 1X500 ml, 10X100 ml.

Not all package sizes are marketed.

6.6 Special precautions for disposal and other handling

Ultravist should be warmed to body temperature prior to use (see section 4.2).

6.6.1 Visual inspection

Contrast media should be visually inspected prior to use and cannot be used if severely discoloured, nor in the presence of particles (particularly crystals) or if the packaging is damaged. As Ultravist is a highly concentrated solution, crystallisation (milky/cloudy appearance and/or sediment at the bottom or floating crystals) may occur in very rare cases.

6.6.2 Vials/bottles

The contrast medium solution should not be aspirated 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 from reaching the solution. The use of cannulas with a long tip and a maximum diameter of 18G is recommended for piercing the stopper and aspirating the contrast medium (cannulas with a lateral aperture, e.g. Nocore-Admix cannulas, are particularly suitable).
Any remaining contrast solution not used in the examination for a given patient must be discarded.

6.6.3 Recipients of large amounts (reserved for intravascular administration)

The following rules apply to the repeated removal of contrast medium from 200 mL and larger containers:

The repeated removal of the contrast medium should be carried out using a device approved for multiple use only.
The rubber stopper of the bottle must never be pierced more than once to avoid large amounts of microparticles from the stopper reaching the solution.
The contrast medium must be administered using an automatic delivery system (automatic injection device), or by another approved procedure that ensures sterility of the contrast medium.
To prevent cross contamination, the tube from the injector to the patient (patient's tube) must be replaced after every patient.
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.
The instructions of the device manufacturer must be followed.
All unused Ultravist product in opened containers must be discarded ten hours after first opening the container.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 4527702

8. MANUFACTURER

Bayer A.G., Mullerstr. 170-178, Berlin, Germany

9. MARKETING AUTHORISATION NUMBER(S)

Ultravist 300: 064-18-27492-00
Ultravist 370: 064-19-27493-00

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