SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Ultravist® 370, Injectable solution, 76.9% (37% iodine)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml Ultravist® 370 contains 768,86 mg iopromide (equivalent to 370 mg iodine)

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injectable solution

Clear, colorless to pale yellow solution.

Ultravist has the following physical-chemical properties at various concentrations:

Iodine concentration (mg/ml)	**370**
Osmotic mole content (osm/kg H_2O) at 37°C	0.77
Viscosity at 20°C at 37°C	 22.0 10.0
Density at 20°C at 37°C	 1.409 1.399
pH Value	6.5-8.0

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

This product is for diagnostic use only.

For contrast enhancement. For intravascular use and use in body cavities.

Ultravist 370:

Intravenous pyelography
Angiocardiography
Computerized Tomography
Digital Subtraction Angiography
Contrast enhancement of cavities (except for myelography, ventriculography and cerebral ventricles radiography)

for use in adult women in contrast-enhanced mammography to evaluate and detect known or suspected lesions of the breast, as an adjunct to mammography (with or without ultrasound) or as an alternative to magnetic resonance imaging (MRI) when MRI is contraindicated or unavailable.

Ultravist is not recommended for intrathecal use.

4.2. Posology and method of administration

General Information

Warning before use

The contrast agent that has been warmed to body temperature is better tolerated and can be more easily infused due to reduced viscosity.

For additional information see section 6.6 "Use/Handling Instructions"

Posology

Posology for intravascular use

Dosage must be individualized depending on the age, the weight, the clinical request and the examination technique.

The dosages referenced herein below are indicative and refer to the usual doses for adults with average weight 70kg. The doses are given as single injections or per kilogram of body weight, as advised herein below.

Doses up to **1.5 g iodine per kilogram of body weight** are generally well tolerated.

Recommended Dosage for single injections:

Conventional angiography

Thoracic aortography	50-80 ml Ultravist 370
Angiocardiography	
Cardiac ventricles	40-60 ml Ultravist 370
Intracoronary	5-8 ml Ultravist 370

Intravenous Digital Subtraction Angiography (DSA)

The intravenous single injection (bolus) 30-60 ml Ultravist 370 (flow time: 8-12 ml/s into royal vein, 10-20 ml/sec into vena cava) is recommended only for imaging of large torso vessels. The amount of the contrast agent remaining at contact with the vascular wall may be reduced and diagnostically serve with single (bolus) injection 20-40 ml of physiological solution of sodium chloride immediately afterwards.

Adults:
30-60 ml Ultravist 370

Intraarterial Digital Subtraction Angiography (DSA)
The dosages and the concentrations used at the conventional angiography may be reduced when used for intraarterial digital subtraction angiography.

Computerized Tomography (CT)
When possible, Ultravist must be intravenously infused by single injection (bolus), preferably using an infusion device. Only when tomography is slow, half the total dose should be administered as single (bolus) injection and the remaining within 2-6 minutes, so that a relatively stable – if not maximum – blood concentration be achieved.
Helicoid computerized tomography, in a single filming, but mainly in multiple section technique, allows the fast intake of many data during one breath holding. Using a stable infusion device at bolus administration is particularly recommended in order to optimize the imaging outcome of the administered intravenous single (bolus) injection at the area of concern (maximum rate, time and term of reinforcement).

- *Full-Body Computerized Tomography*

During full-body computerized tomography, the required contrast agent doses and the administration rate depend on the organs examined, the diagnostic issue, but mainly from the variable times of tomography and imaging of the equipment available.

- *Cerebral Computerized Tomography*

Adults
Ultravist 370: 1- max 1.5 ml/kg of body weight

Contrast-enhanced mammography (CEM)
Ultravist should be injected intravenously, preferably using a power injector. The image acquisition starts approximately 2 minutes after the administration of contrast media.
Adults:
Ultravist 370: 1.5 ml/kg BW

Intravenous Urography

The normal inability to condensate the still immature nephron of the children's kidneys requires relatively high doses of contrast agent.

The following doses are recommended:

Newborns (<1 month)	1.2 g iodine/kg BW = 3.2 ml/kg BW Ultravist 370
Infants (1 month-2 yrs)	1.0 g iodine/kg BW = 2.7 ml/kg BW Ultravist 370
Children (2-11 yrs)	0.5 g iodine/kg BW = 1.4 ml/kg BW Ultravist 370
Adolescents & Adults	0.3 g iodine/kg BW = 0.8 ml/kg BW Ultravist 370

*BW: Body Weight

The dose may be increased in adults if considered necessary under special conditions.

Filming times

The above mentioned guiding Ultravist 370 dosages being observed, for infusion term of 1-2 minutes, the nephric parenchyma appears most of the times, at more intense contrasting, 3-5 minutes after start of administration while the nephric pelvis with the drainage outflows, 8-15 minutes after start of administration. In case of younger patients, the shortest time must be selected while in cases of elderly patients, the most deferred time.

Normally, the first film is recommended about 2-3 minutes after the contrast agent's administration. In cases of newborns, toddlers and patients with limited nephric function, deferred filming times may give enhanced imaging of the urinary system

Dosage for use in other body cavities

When conducting arthrography and during endoscopic retrograde cholangio-pancreatography (ERCP) the administration of the contrast agent must be monitored via radioscopy.

Recommended doses for single examinations:

Dosage may vary depending on the age, the weight and the overall condition of the patient. Also, depending on the clinical issue, the examination technique and the body area examined.

Indicatively, the recommended average dose for adults is as follows:

Arthrography: 5-15 ml Ultravist 370.

ERCP: Dosage usually depends on the clinical request and the size of the area to be imaged.
Other: Dosage usually depends on the clinical request and the size of the area to be imaged.

Additional information regarding special populations

- Newborns (<1 month) and infants (1 month – 2 yrs)

Infants <1 year and especially the newborns (1 month – 2 yrs) are very sensitive to the variations of the electrolytes and the hemodynamic fluctuations. Attention should be paid to the contrast agent dose to be administered, the technique for conducting the radiology process and the patient's condition.

- Elderly (over 65 yrs)

During clinical study, no differences were noted in iopromide's pharmacokinetics among elderly (over 65 yrs) and younger patients. Consequently, no particular indications for dose adjustment in elderly patients is given, except for those described in the "Posology" section.

- Patients with hepatic deficiency

Iopromide's excretion is not affected from any liver malfunction since iopromide is not metabolized and only approximately 2% is excreted via faeces. No dose adjustment is considered necessary to patients with reduced hepatic function.

- Patients with renal deficiency

Since iopromide is excreted almost exclusively in invariable form via the kidneys, the iopromide elimination is extended in patients with reduced renal function. The minimum dose possible must be used in patients with pre-existing impaired renal function so as to reduce the risk of additional impairment in renal function, caused by the contrasting media (see also para.4.4. "Special warnings and precautions for use" and 5.2. "Pharmacokinetic properties").

4.3. Contraindications

No absolute contraindications exist for Ultravist use.

4.4. Special warnings and precautions for use

For all indications:

- *Oversensitivity Reactions*

Ultravist may be correlated to anaphylactic reactions / oversensitivity or other idiosyncratic reactions involving cardiovascular, respiratory and skin conditions.

Allergic reactions mild to severe, including shock, are possible (see section 4.8 “Undesirable Effects”) Most of these actions appear within 30 minutes since administration. However, delayed reactions might appear (hours or even days later).
The risk for oversensitivity reactions is higher in case of:

- Prior reaction to contrast mean,
- History of bronchial asthma or other allergic disorders

Especially in patients with known oversensitivity to Ultravist or any of its excipients, or having history of previous reaction to any other iodine contrasting agent, careful assessment of the risk-benefit relation is required due to increased risk of oversensitivity reactions (including severe reactions).
Nevertheless, such reactions do not appear at a standard rate and their nature cannot be anticipated.
Patients presenting similar reactions while receiving b-receptor excluders might demonstrate endurability in therapeutic medication with b-receptors agonists (see also para. 4.5 “Special warnings and precautions for use”).
In case of severe oversensitivity reaction, the cardiovascular disease patients are more prone to severe even fatal outcome.
Due to possibility of serious oversensitivity post-administration reactions, the patient should be monitored after the examination.
Preparedness for institution of emergency measures is necessary for all patients. In patients with increased risk of acute allergic reactions and patients with history of medium or severe acute reaction, asthma or allergy that required medical treatment, a prophylactic medication with corticosteroids may be considered.

- *Thyroid Gland Malfunction*

Highly careful assessment of the risk/benefit relation is necessary in patients with known or suspected hyperthyroidism or goiter since the iodine containing contrasting agents might cause hyperthyroidism and thyrotoxic crisis to such patients. Controlling the thyroid function before Ultravist administration and /or preventive medication with anti-thyroids might 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 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.

Paediatric population:

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 paediatric patients younger than 3 years.

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 paediatric intensive care units, and congenital cardiac conditions are associated with an increased risk of hypothyroidism after ICM exposure. Paediatric 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.

- *Central Nervous System (CNS) Diseases*

Patients with history of CNS disorders might be under higher risk of neurological implications related to Ultravist administration. Neurological implications appear more often in the cerebral angiography and relevant procedures.

Encephalopathy has been reported with the use of iopromide (see section 4.8). Contrast encephalopathy may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema. Symptoms usually occur within minutes to hours after administration of iopromide and generally resolve within days.

Attention should be given to situations when the threshold as to epileptic crises is lowered due to previous history of epileptic crises and use of certain simultaneously administered medicines.

The factors that increase permeability of the blood-brain barrier facilitate the transition of the contrasting agent into the cerebral tissue which might result to CNS reactions, for instance encephalopathy.

If contrast encephalopathy is suspected, appropriate medical management should be initiated and administration of iopromide must not be repeated.

- *Hydration*

Adequate hydration status must be assured in all patients before and after intravascular and or intrathecal Ultravist administration (see also the sub-section: "intravascular use – renal deficiency"). This applies particularly to patients with multiple myeloma, diabetes, polyurea, oliguria, hyperuricemia as well as in newborns, infants, toddlers 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.'

- *Inquietude*

Intense situations of excitement, inquietude and pain may increase the risk of undesired actions or even intensify the reactions related to contrast agents. Care should be taken for minimizing the stress conditions in such patients.

- *Preliminary Control*

No sensitivity test is recommended by using a small test dose of the contrasting agent since this has no prognostic value. Additionally, the sensitivity tests themselves have occasionally led to sever or even fatal oversensitivity reactions.

- *Severe cutaneous adverse reactions (SCARs)*

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported with unknown frequency in association with iopromide administration.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions.

In children, the initial presentation of a rash can be mistaken for an infection, and physicians should consider the possibility of a reaction to iopromide in children that develop signs of rash and fever.

Most of these reactions occurred within 8 weeks (AGEP 1-12 days, DRESS 2-8 weeks, SJS/TEN 5 days up to 8 weeks).

If the patient has developed a serious reaction such as SJS, TEN, AGEP or DRESS with the use of iopromide, iopromide must not be readministered in this patient at any time.

Intravascular Use

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

The risk factors indicatively include:

- pre-existing renal insufficiency (see subsection '4.2.3.4 Patients with renal impairment'), Dehydration (see subsection '4.4.1.4. Hydration'),
- Diabetes
- Multiple myeloma, paraproteinemia
- Repeated and/or high doses 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').The patients subjected to hemodialysis even if not demonstrating deficient renal function, may receive Ultravist for conducting radiology examinations since the iodine contrast agents are excreted via hemodialysis procedure.

- *Cardiovascular disease*

Patients with significant heart disease or coronary disease are under increased risk to develop clinically significant hemodynamic variations and arrhythmia.

The intravascular injection Ultravist might result in lung edema in patients with heart deficiency.

- *Phaeochromocytoma*

Patients with phaeochromocytoma may be under increased risk to develop hypertension crisis.

- *Gravis Muscular Diseases*

Administration of Ultravist might deteriorate the symptoms of Gravis muscular disease.

- *Thromboembolic Events*

One of the non-ionic contrast agents' properties is their little influence on the normal functions of the organization. Therefore, the non-ionic contrast media have less anti-coagulant *in vitro* effect than the ionic ones. Many factors, in addition to the contrast media, including transparency of the procedure, the number of injections, the catheter's and the syringe's material, the underlying disease and the simultaneous medication may contribute to occurrence of thromboembolic episodes. This must be considered at the application of vein-catheter techniques and

particular attention must be given to the angiography's technique and the frequent wash-up of catheters with physiological solution (if necessary, with heparin) while the examination's duration should be reduced to the minimum, so as to minimize the risk of the procedure-related thromboses and embolisms.

Contrast-enhanced mammography (CEM)

Contrast-enhanced mammography results in higher patient exposure to ionizing radiation than standard mammography. Radiation dose depends on breast thickness, the type of mammographic device and the device's system settings. The overall CEM radiation dose remains under the threshold defined by international guidelines for mammography (below 3 mGy).

4.5. Interactions with other pharmaceutical products and other forms of interaction

Biguanides (metformin): In patients with acute renal deficiency or severe renal disease, the biguanides' excretion might be reduced with the result to be accumulated and develop lactic acidosis (see para.4.4. sub-section "intravascular use-Renal Deficiency"). According to the measurements of renal function, the possible need for preventive interruption of the metformin administration should be considered, 48 hours before and after the administration of the contrast agent.

- *Interleukin-2:* precedent therapy (up to 2 weeks) with interleukin-2 is correlated to increased risk of decelerated type reactions to Ultravist.
- *Radioisotopes:* Diagnosis and therapy of the thyroid gland disorders with radioisotopes taken in via the thyroid gland might be obstructed for up to several weeks after the administration of Ultravist, due to reduction of the thyroid tissue ability to intake the radioisotopes.

4.6. Pregnancy and Lactation

Pregnancy

No sufficient and well-controlled studies have been conducted in pregnant women. No sufficient proof exists that there is no risk from administration of non-ionic contrasting agents in pregnant patients. Given that, when possible, the exposure to the radiation must be avoided during pregnancy, the benefits from the X-ray examination with or without contrasting agent must be carefully balanced against the possible risk. Studies in experimental animals do not indicate harmful effects related to pregnancy, fetus' development, labor or post-birth development, following the administration of iopromide to humans for diagnostic purposes.

Breastfeeding

Whether Ultravist is safe for breastfed babies has not been studied. The contrast agents are slightly excreted into mother's milk. The harm to the breastfed baby is not possible (see also section4.4, sub-section "Intravascular use-Renal Deficiency".

4.7. Effects on ability to drive and use machines

No data available.

4.8. Undesired Effects

Summary of the Safety Profile

The total safety profile of Ultravist is based on data obtained in pre-marketing studies from more than 3.900 patients and post-marketing studies in more than 74.000 patients, as well as data from spontaneous reporting and bibliography.

The most frequently undesired effects (≥4%) in patients receiving Ultravist is headache, nausea and vasodilation.

The most severe undesired effects in patients receiving Ultravist is anaphylactic shock, respiratory arrest, bronchospasm, laryngeal edema, pharyngeal edema, asthma, coma, cerebral infarction, stroke, cerebral edema, spasms, arrhythmia, cardiac arrest, myocardial ischemia, myocardium infarction, heart deficiency, bradycardia, cyanosis, hypotension, shocl, dyspnea, lung edema, respiratory deficiency and aspiration.

List of undesired effects in table

The undesired effects noted from Ultravist are presented in the following table. They are categorized according to the Organic System as per MedDRA (version 13.0). The most appropriate MedDRA term is used to described also a specific condition as well as its synonyms and related conditions.

The undesired effects from the clinical studies are categorized depending on their 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'.

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

Organic System	Common	Uncommon	Rare	Not Known
Immunization System Disorders		Hypersensitivity reactions/anaphylactoid reactions (anaphylactic shock§)*), respiratory arrest§)*), bronchospasm*), laryngeal*)/pharyngeal*) edema, facial edema, tongue edema§), laryngeal/pharyngeal spasm§), asthma§)*, conjunctivitis§), lacrimation§), sneezing, coughing, mucosal edema, rhinitis§), hoarseness§), throat irritation§)*), urticaria, itching, angioedema)		
Endocrine Disorders				Thyrotoxic crisis, thyroid disorder
Psychiatric Disorders			Inquietude	
Nervous System Disorders	Dizziness, Headache, Dysgeusia	Vasovagal reactions,, confusional state, nervousness, paresthesia/hypesthesia, somnolence		Coma*), cerebral ischemia/infarction*), stroke*), cerebral edema a)*), spasms*), transient cortical blindness a), loss of consciousness, agitation, amnesia, tremor, speech disorders, paresis/paralysis, Contrast encephalopathy
Eye Disorders	Blurred/ disturbed vision			
Ear and Labyrinth Disorders				Hearing Disorders
Cardiac Disorders	Chest Pain / Malaise	Arrhythmia*)	Cardiac arrest *), Myocardial ischemia, Pulse sensation	Myocardium Infarction*), Cardiac failure*), Bradycardia*), Tachycardia, Cyanosis*)
Vascular Disorders	Hypertension/ Vasodilation	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 glands enlargement, diarrhea

Skin and subcutaneous tissue disorders				Bullous conditions (i.e. Stevens-Johnson or Lyell syndrome), , rash, erythema hyperhydrosis, acute generalised exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms
Musculoskeletal, and connective tissue disorders				Compartment syndrome in case of extravasation[a)]
Renal & urinary pathways disorders				Renal impairment [a)], acute renal failure [a)]
General disorders and administration site conditions	Pain, injection site reaction (various kinds i.e. pain, warmth[§)], edema[§)], inflammation[§)] and soft tissue injury[§)] in case of extravasation) Feeling hot	Edema		Malaise, Chills, Pallor
Investigations				Fluctuations in body temperature

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

The majority of the reactions after myelography or use in body cavities appear several hours after administration. Except for the above-mentioned undesired effects the following might appear when used in ERCP: increase of the enzyme level of the pancreas and pancreatitis at an unknown frequency.

Reporting suspected undesired effects

Reporting any suspected undesired effects after the provision of a marketing license of the pharmaceutical product is important. It allows the constant monitoring of the benefit-risk relation of the pharmaceutical product. The professionals of the healthcare sector are requested to report any suspected undesired effects via the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9. Overdose

The results of acute toxicity studies on experimental animals do not indicate risk of acute poisoning when using Ultravist.

The symptoms may include liquid and electrolytes disturbance, renal deficiency, cardiovascular and pneumonic complications.

In case of non-voluntary intravascular overdose the liquids, electrolytes and renal operation is recommended. Overdoes treatment must focus on the support of vital functions.

Ultravist might be removed via hemolysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Water soluble, nephrotropic, of low osmolarity, contrast agents for X-Rays.

ATC Code : V08AB05

The contrast substance contained in Ultravist is iopromide, a non-ionic water-soluble derivative of the triply iodized isophthalic acid with molecular weight 791.12 at which the strongly connected iodine absorbs the X-Rays.

Infusion of Ultravist makes non-transparent those vessels or body cavities at the course of the contrast agent's flow, allowing the radiographic imaging of the internal structures until significant dilution occurs.

Contrast-enhanced mammography (CEM)

Nine studies, including 1,531 patients, were focused on the diagnostic performance in relevant settings.

In studies evaluating suspicious lesions, CEM showed a sensitivity, ranging from 96.9% to 100%, and a specificity, ranging from 69.7% to 87%, compared to digital mammography with a sensitivity of 96.9% and a specificity of 42.0%.

In studies evaluating the accuracy of CEM compared to other diagnostic modalities, CEM showed a sensitivity of 100% and a negative predictive value (NPV) of 100% in comparison to MRI (93% and 65%, $p=0.04$ and $p <0.001$, respectively). When compared to full field digital mammography (FFDM) combined with ultrasound, CEM showed a sensitivity of 92.3% vs 89.8%, $p<0.05$, positive predictive value (PPV) (93% vs 88.7%, $p<0.01$) and accuracy (90.2% vs 87%, $p<0.05$).

In patients with MRI contraindications, both mammography and CEM classification correlated significantly with histopathological classification. CEM showed a sensitivity of 98.8% and a specificity of 54.55% vs. 89.16% and 36.36% respectively for mammography.

In studies evaluating the pre-surgical assessment and staging of breast cancer, CEM demonstrated a sensitivity, specificity, PPV, NPV and accuracy of 93%, 98%, 90%, 98% and 97%, respectively. CEM altered the established surgical plan in 18.4% of cases.

5.2. Pharmacokinetic properties

General information

Iopromide behaves in the organism as any other highly hydrophile biologically inactive compound that is excreted from the kidneys (i.e. mannitol or inulin)

- *Absorption and Distribution*

Following intravenous administration, the iopromide concentrations in the plasm are very rapidly reduced due to the distribution in the extracellular area and the following excretion. The total allocation volume at stabilized status is approximately 16 L that approximately equals the extracellular area.

The proteinic blockage is neglectable (almost 1%). There is no sign that iopromide penetrates the intact blood-brain barrier. In studies with animals, a small quantity penetrated the placenta (≤ 0.3% of the dose was found at rabbit fetuses).

Following the administration to the bile and/or the pancreatic duct during endoscopic retrograde cholangio-pancreatography (ERCP), the iodine contrast agents are systematically absorbed and reach the maximum concentrations in the plasm between 1 and 4 hours after the administration. The maximum iodine levels at the serum after average dose of almost 7.3 g iodine, was almost 40 times lower than the maximum serum levels after respective intravenous doses.

- *Metabolism*

Iopromide is not metabolized.

- *Elimination*

The final half-life term of iopromide is almost 2 hours, regardless the dose.

Within the width of dosage checked, the average total clearance of iopromide amounts up top 106 ± 15 ml/min, similarly with the renal clearance of 102 ± 15 ml/min. Consequently, the iopromide excretion is almost exclusively renal. Only almost 2% of the administered dose is excreted via the faeces within 3 days.

Approximately 60% of the dose is excreted within 3 hours following the intravenous administration via urine. Average ≥93 % of dose was regained within 12 hours. The excretion is actually completed within 24 hours.

Following the administration to the bile or/and the pancreatic duct during ERCP the iodine concentrations in the plasm, returned to the levels before dose, within 7 days.

- *Linearity – Non-linearity*

The pharmacokinetic factors of iopromide in humans change depending on the dose (i.e. C_{max1} AUC) or is irrelevant of the dose (i.e. $V_{ss1}t_{1/2}$).

- *Features at the special patient populations*

Elderly (over 65 years)

Middle-age patients (49-64 years) and aged patients (65-70 years) without significant renal deficiency had total serum clearance between 74 and 114 ml/min (middle-age group, average 102 ml/min) and between 72 and 110 ml/min (elderly group, average 89 ml/min) that was only marginally lower than in younger patients (88 to 138 ml/min, average 106 ml/min). The isolated half-life terms were between 1.9-2.9 hours and 1.5 and 2.7 hours respectively. Compared to the range of 1.4 to 2.1 hours in young healthy volunteers, the final half-life terms were similar. The small differences relate to the normal reduced rate of the glomerular infiltration over the age.

Pediatric Population

Iopromide's pharmacokinetics has not been explored in the pediatric population (see paragraph 4.2 "Dosage and mode of Administration").

Patients with renal deficiency

In patients with reduced renal function, the half-life term of iopromide is extended according to the reduced glomerular infiltration rate. The plasm clearance was reduced to 49. ml/min / 1.73 m^2 (CV=53%) in patients with mild and moderately affected renal function (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 severely affected renal function not dependent on hemodialysis (CL_{CR}=30-10 ml/min / 1.73 m^2).

The final average half-life term was 6.1 hours (CV = 43%) in patients with mild and moderately affected renal function (80≥CL_{CR}>30 ml/min / 1.73 m^2) and 11.6 hours (CV = 49%) in the patients with severely affected renal function not dependent on hemodialysis (CL_{CR}=30-10 ml/min / 1.73 m^2).

The quantity regained at the urine within 6 hours following the dose, was 38% in the patients with moderately affected renal function and 26% in patients with severely affected renal function, compared to over 83% of the young volunteers. Within 24 hours following the dose, the regain as 60% in patients with moderately affected renal function and 51% in patients with severely affected renal function, compared to over 95% of the young volunteers.

Iopromide may be removed via hemodialysis. Approximately 60% of the iopromide dose is removed during 3-hour hemodialysis.

Patients with hepatic deficiency

Excretion is not affected by hepatic function deficiency since iopromide is not metabolized and only approximately 2% of the dose is excreted via faeces.

5.3. Preclinical safety data

Based on the conventional studies results on pharmaceutical safety, toxicity following repeated doses, genotoxicity and toxicity during reproduction, preclinical data revealed no risk for humans.

- *Systematic toxicity*

  Experimental studies on animals for assessing systematic tolerance to repeated daily intravenous administration have not given any findings prohibitive to the usual, isolated administration to humans.

- *Genotoxic potential, tumor generation*

  In studies about genotoxic activity (mutilation tests in genes and chromosomes), iopromide demonstrated no mutilating action in vitro or in vivo. Based on the absence of genotoxic effects and considering metabolic stability, the pharmacokinetics data and the absence of signs of toxic effect in rapidly developing tissues as well as the fact that Ultravist was administered only once, no risk of tumor generating action in humans seems to exist. Local tolerance and possibility of sensitization from contact.

  Studies of local tolerance following single and repeated intravenous administration and following single intraarterial, intramuscular, near-vein, intraperitoneal, intraspinal administration and administration on the conjunctiva, demonstrated that none or only light undesired local effects should be expected in blood vessels, near-vein tissues, subarachnoid area or on human mucosa. Studies of possible sensitization from contact did not reveal any potential sensitization.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium Calcium Edetate, Trometamol, Hydrochloric acid 10% (for pH adjustment), sodium hydroxide (for pH adjustment), water for injection

6.2. Incompatibilities

Ultravist must not be mixed with other medicines in order to avoid the risk of possible incompatibility.

6.3. Shelf life

3 years. Once opened, Ultravist is recommended to be used within 10 hours.

6.4. Special precautions for storage

Store below 25ºC, in a place protected from light and radiation

Keep medicines carefully and out of the reach of children.

6.5. Nature and contents of container

Glass bottles type II

Glass vialstype I

Rubber stopper: chlorobutyl or bromobutyl elastomer, grey

Ultravist® 370

Greece: 50 ml, 100 ml vials and 150 ml, 200 ml and 500 ml, 1000 ml bottles

Cyprus: 50 ml, 100 ml vials and 150 ml, 200 ml και 500 ml, 1000 ml bottles

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

- *Visual inspection*

Before using the contrast agents a visual inspection must be carried and they should not be used in case of discoloration, in case particles (crystals included) are present or in case of a defective container.

Since Ultravist is a high-concentration solution, crystallization may very rarely appear (milky – blurry appearance and/or sediment at the bottom or pending crystals).

- *Vials*

The contrast agent solution should be drawn into the syringe or in the solution of the infusion device only right before its administration.

The flexible cap should be pierced only once, so as to avoid inflow of particles via the cap into the solution. For piercing the flexible cap and drawing the contrast agent long obliquely cut needles are recommended with maximum diameter 18G (highly appropriate are the genuine puncture needles with oblique opening i.e. Nocore-Admix needles).

Any contrast medium solution not used in one examination for a specific patient must be discarded

- *Large volume containers (only for intravascular use)*

The below instructions must be followed for multiple removal of contrast agent from the packs over 200ml:

Multiple removal of contrast agent should take place by using medical technological apparatus approved for multiple use.

The flexible cap must be pierced only once, to avoid inflow of particles via the cap into the solution.

The contrast agent must be administered assisted by automatic infuser or any other procedure that can safeguard contrast agent’s sterility.

The tube leading from the infuser to the patient (patient's tube) must change after each examination since this is infected with the patient's blood.
The tubes and all disposable infuser accessories must be discarded when the bottle empties or 10 hours after the container's first opening.
The contrast agent remaining in an opened bottle must be discarded ten hours after the container's first opening.
In addition, any additional instructions given by the manufacturer of the respective equipment must be faithfully complied with.

7. MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder in Greece and Cyprus
Bayer Hellas S.A.
6-8 Agisilaou Street, 151 23 Marousi, Attiki, GreeceTel. 2106187500
Local Representative in Cyprus
Novagem Ltd
Tel. 00357 22483858

8. MARKETING AUTHORIZATION NUMBER

MA1354/00401

9. DATE OF FIRST APPROVAL/RENEWAL OF AUTHORIZATION

6th February 2007 / 10th October 2012

10. DATE OF TEXT REVISION

02/2025

ANNEXES

Annex 1

Excipients

This pharmaceutical product contains less than 1 mmol (23mg) of sodium per dose (based on the average of the quantity given to a 70kg human), i.e. essentially "sodium-free".