Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ultravist 240mg/ml Solution for Injection (50ml)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultravist 240: 1ml contains 499mg iopromide, equivalent to 240mg iodine.
One 50ml bottle contains 24.95g iopromide.

This medicinal product contains 12.3 micrograms sodium per ml.

For a full list of excipients, *see Section 6.1*.

3 PHARMACEUTICAL FORM

Solution for injection
Clear, colourless to pale yellow aqueous solution.

The physico-chemical properties of Ultravist at the concentrations listed below are:

Iodine concentration (mg/ml)	240	300	370
Osmolality (osm/kg H_2O) at 37 °C	0.48	0.59	0.77
Viscosity (mPa.s) at 20 °C at 37 °C	4.9 2.8	8.9 4.7	22.0 10.0
Density (g/ml) at 20 °C at 37 °C	1.263 1.255	1.328 1.322	1.409 1.399
pH-value	6.5-8.0	6.5-8.0	6.5-8.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

Ultravist 240: For intravascular use and use in body cavities.
Contrast enhancement in computerised tomography (CT), digital subtraction angiography (DSA), intravenous urography, phlebography of the extremities, visualisation of body cavities (e.g. arthrography, hysterosalpingography, fistulography) with the exception of myelography, ventriculography, cisternography.

4.2 Posology and method of administration

General information

Warning prior to use

Contrast media which are warmed to body temperature before administration are better tolerated and can be injected more easily because of reduced viscosity.

For additional instructions see section 6.6.

- **Dosage regimen**

Dosage for intravascular use

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 in accordance with the clinical situation. Dosage should be adapted to age, weight, cardiac output, clinical question, examination technique and the nature and volume of the vascular 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 kilo (kg) body weight (BW) as indicated below.

Generally, doses of up to 1.5 g iodine per kg body weight are well tolerated.

After the administration, the patient should be kept under observation for at least 30 minutes, since experience shows that the majority of all severe incidents occur within this time.

Recommended doses for single injections:

Conventional angiography

Aortic arch angiography	50-80 ml Ultravist 300
Selective angiography	6-15 ml Ultravist 300
Thoracic aortography	50-80 ml Ultravist 300/370
Abdominal aortography	40-60 ml Ultravist 300
Arteriography: Upper extremities Lower extremities	 8-12 ml Ultravist 300 20-30 ml Ultravist 300
Angiocardiography: Cardiac ventricles Intracoronary	 40-60 ml Ultravist 370 5-8 ml Ultravist 370
Venography: Upper extremities or Lower extremities or	 50-60 ml Ultravist 240 15-30 ml Ultravist 300 50-80 ml Ultravist 240 30-60 ml Ultravist 300

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

Adults:
30 – 60 ml Ultravist 300/370

Intraarterial DSA
Intraarterial digital subtraction angiography requires smaller volumes and lower iodine concentrations than the intravenous technique. The more selective the angiography is, the lower the dose of contrast medium can be. The values used in conventional angiography for bolus concentration, bolus volume and flow rate can be reduced for intraarterial DSA.

Computerized tomography (CT)
Whenever possible, Ultravist should be injected as an i.v. bolus, preferably using a power injector. Only for slow scanners about half of the total dosage should be administered as a bolus and the rest within 2 – 6 minutes to guarantee a relatively constant – though not maximum – blood level.
Spiral CT in single but especially in multi-slice technique allows the rapid acquisition of a volume of data during single breath-hold. To optimize the effect of the i.v. administered bolus (80 – 150 ml Ultravist 300) in the region of interest (peak, time and duration of enhancement), the use of an automatic power injector and bolus tracking is strongly recommended.

Whole body CT
In computerized tomography, the necessary doses of contrast medium and the rates of administration depend on the organs under investigation, the diagnostic problem and, in particular, the different scan and image reconstruction times of the scanners in use.

Cranial CT
Adults:
Ultravist 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

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

The following dosages are recommended.

Newborns (< 1 month)	1.2 g I/kg BW	= 5.0 ml/kg BW Ultravist 240 = 4.0 ml/kg BW Ultravist 300 = 3.2 ml/kg BW Ultravist 370
Infants (1 month-2 years)	1.0 g I/kg BW	= 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 BW	= 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 BW	= 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 administered 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 in the case of 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 visualization of the urinary tract.

Dosage for use in body cavities
During arthrography and hysterosalpingography, 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 – 10 ml Ultravist 240/300/370

Hysterosalpingography
10 – 25 ml Ultravist 240

Other
Dosage depends generally on the clinical question and the size of structure to be imaged.

- **Additional information on special populations**

Newborns and infants
Young infants (age <1 year) and especially newborns are susceptible to electrolyte imbalance and hemodynamic alterations. Care should be taken regarding the dose of contrast medium to be given, the technical performance of the radiological procedure and the patient status.

Elderly population (aged 65 years and above)
In a clinical study, no differences in pharmacokinetics of iopromide were observed between elderly (aged 65 years and above) and younger patients. Therefore, no specific recommendation for a dosage adjustment is given for elderly patients beside those described in subsection ‘Dosage regimen’. These general dose recommendations should not be exceeded, as the glomerular filtration rate might be physiologically slightly reduced in elderly subjects, thus increasing the risk of renal impairment aggravation by iodinated contrast agents.

Patients with hepatic impairment
Elimination of iopromide is not affected by impaired liver function as only about 2% of the dose is eliminated via feces and iopromide is not metabolized. No dosage adjustment is considered necessary in patients with hepatic impairment.

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 and 5.2).

4.3 Contraindications

Manifest hyperthyroidism.

Use in patients with a history of serious hypersensitivity to iopromide.

4.4 Special warnings and precautions for use

For all indications

- **Hypersensitivity reactions**

Ultravist can be associated with anaphylactoid / hypersensitivity (see section 4.3) or other idiosyncratic reactions characterized by cardiovascular, respiratory and cutaneous manifestations.

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

The risk of hypersensitivity reactions is higher in case of:
- previous reaction to contrast media
- history of bronchial asthma or other allergic disorders.

Particularly careful risk/benefit judgement is required in patients with known hypersensitivity to Ultravist or any excipient of Ultravist, or with a previous hypersensitivity reaction to any other iodinated contrast medium due to an increased risk for hypersensitivity reactions (including severe reactions).

However, such reactions are irregular and unpredictable in nature.

Patients who experience such reactions while taking beta blockers may be resistant to treatment effects of beta agonists (see also section 4.5).
In the event of a severe hypersensitivity reaction, patients with cardiovascular disease are more susceptible to serious or even fatal outcomes.
Due to the possibility of severe hypersensitivity reactions after administration, post-procedure observation of the patient is recommended.
Preparedness for institution of emergency measures is necessary for all patients.

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

- **Thyroid dysfunction**

Iodinated contrast media may induce hyperthyroidism and thyreotoxic crisis in patients with hyperthyroidism or goiter. Testing of thyroid function prior to Ultravist administration and/or preventative thyreostatic medication may be considered in patients with suspected hyperthyroidism.

In neonates, especially preterm infants, who have been exposed to Ultravist, either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function, as an exposure to excess iodine may cause hypothyroidism, possibly requiring treatment.

- **CNS disorders**

Patients with CNS disorders may be at increased risk to have neurological complications in relationship to Ultravist administration. Neurological complications are more frequent in cerebral angiography and related procedures.
Caution should be exercised in situations in which there may be a reduced seizure threshold, such as a previous history of seizures and the use of certain concomitant medication.
Factors which increase blood-brain barrier permeability facilitate the passage of the contrast medium into cerebral tissue, possibly leading to CNS reactions.

- **Hydration**

Adequate hydration must be assured before and after intravascular and intrathecal Ultravist administration in order to minimize the risk of contrast media-induced nephrotoxicity (see also subsection ‘Intravascular use’ – ‘Renal impairment’). This applies especially to patients with multiple myeloma, diabetes mellitus, polyuria, oliguria, hyperuricemia, as well as to newborns, infants, small children and elderly patients.

- **Anxiety**

Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium-related reactions. Care should be taken to minimize the state of anxiety in such patients.

- **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.

<u>Intravascular use</u>

- **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, e.g.:
pre-existing renal insufficiency,
dehydration,
diabetes mellitus,
multiple myeloma / paraproteinemia,
repetitive and / or large doses of Ultravist.
Adequate hydration must be ensured in all patients who receive Ultravist administration.
Patients on dialysis, if without residual renal function, may receive Ultravist for radiological procedures as iodinated contrast media are cleared by the dialysis process.

- **Cardiovascular disease**

Patients with significant cardiac disease or severe coronary artery disease are at an increased risk of developing clinically relevant haemodynamic changes and arrhythmia.
The intravascular injection of Ultravist may precipitate pulmonary oedema in patients with heart failure.

- **Pheochromocytoma**

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

- **Myasthenia gravis**

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

- **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 procedures one should be aware of this and pay meticulous attention to the angiographic technique and flush the catheter frequently with physiological saline (if possible with the addition of heparin) and minimize the length of the procedure so as to minimize the risk of procedure-related thrombosis and embolism.

4.5 Interaction with other medicinal products and other forms of interaction

Biguanides (metformin): In patients with acute kidney failure or severe chronic kidney disease biguanide elimination can be reduced leading to accumulation and the development of lactic acidosis. As the application of Ultravist can lead to renal impairment or an aggravation of renal impairment, patients treated with metformin may be at an increased risk of developing lactic acidosis, especially those with prior renal impairment (see section 4.4 – subsection ‘Intravascular use’ – ‘Renal impairment’). Based on measurements of kidney function, the need for an interruption in the metformin administration should be considered.

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

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

The use of certain concomitant medication may reduce the seizure threshold, thus increasing the risk of a contrast medium related reaction (see also section ‘4.4 Special warnings and precautions for use’).

Caution must also be exercised in alcoholics because of the possibility of a reduced seizure threshold.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Lactation
Safety of Ultravist for nursed infants has not been investigated. Contrast media are poorly excreted in human breast milk. Harm to the nursed infant is not likely (see also section 4.4 – subsection 'Thyroid dysfunction').

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Ultravist is based on data obtained in pre-marketing studies in more than 3900 patients and post-marketing studies in more than 74 000 patients, as well as data from spontaneous reporting and the literature.
The most frequently observed adverse drug reactions (≥ 4 %) in patients receiving Ultravist are headache, nausea and vasodilatation.

The most serious adverse drug reactions in patients receiving Ultravist are anaphylactoid shock, respiratory arrest, bronchospasm, laryngeal edema, pharyngeal edema, asthma, coma, cerebral infarction, stroke, brain edema, convulsion, arrhythmia, cardiac arrest, myocardial ischemia, myocardial infarction, cardiac failure, bradycardia, cyanosis, hypotension, shock, dyspnea, pulmonary edema, respiratory insufficiency and aspiration.

Tabulated list of adverse reactions
The adverse drug reactions observed with Ultravist are represented in the table below. They are classified according to System Organ Class (MedDRA version 13.0). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.
Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention:
common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000).
The adverse drug reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under 'not known'.

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

System organ class	Common	Uncommon	Rare	Not Known
Immune system disorders		Hypersensitivity / Anaphylactoid reactions (Anaphylactoid shock§) *), Respiratory arrest§) *), Bronchospasm*), Laryngeal*) / Pharyngeal*) / Face edema, Tongue		

		edema[§)], Laryngeal / Pharyngeal spasm[§)], Asthma[§) *)], Conjunctivitis[§)], Lacrimation[§)], Sneezing, Cough, Mucosal edema, Rhinitis[§)], Hoarseness[§)], Throat irritation[§)], Urticaria, Pruritus, Angioedema)		
Endocrine disorders				Thyrotoxic crisis, Thyroid disorder
Psychiatric disorders			Anxiety	
Nervous system disorders	Dizziness, Headache, Dysgeusia	Vasovagal reactions, Confused state, Restlessness, Paraesthesia / Hypoaesthesia, Somnolence		Coma[*)], Cerebral ischaemia / infarction[*)], Stroke[*)], Brain edema[a) *)], Convulsion[*)], Transient cortical blindness[a)], Loss of consciousness , Agitation, Amnesia, Tremor, Speech disorders, Paresis / Paralysis
Eye disorders	Blurred / Disturbed vision			
Ear and labyrinth disorders				Hearing disorders
Cardiac disorders	Chest pain / discomfort	Arrhythmia	Palpitations, Cardiac arrest[*)], Myocardial ischaemia[*)]	Myocardial infarction[*)], Cardiac failure[*)], Bradycardia[*)], Tachycardia, Cyanosis[*)]
Vascular disorders	Hypertension Vasodilatation	Hypotension[*)]		Shock[*)], Thromboembolic events[a)] Vasospasm[a)]
Respiratory thoracic and mediastinal disorders		Dyspnea[*)]		Pulmonary edema[*)], Respiratory insufficiency[*)], Aspiration[*)]
Gastrointestinal disorders	Vomiting, Nausea	Abdominal Pain		Dysphagia, Salivary gland enlargement, Diarrhoea
Skin and subcutaneous				Bullous conditions

tissue disorders				(e.g. Stevens-Johnson's or Lyell syndrome), Rash, Erythema, Hyperhydrosis
Musculoskeletal, connective tissue and bone disorders				Compartment syndrome in case of extravasation[a)]
Renal and urinary disorders				Renal impairment[a)] , Acute renal failure[a)]
General disorders and administration site conditions	Pain, Injection site reactions (various kinds e.g. pain, warmth[§)], edema[§)], inflammation[§)] and soft tissue injury[§)] in case of extravasation), Feeling hot	Edema		Malaise, Chills, Pallor
Investigations				Body temperature fluctuation

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

[a)] intravascular use only

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

In addition to the adverse drug reactions (ADRs) listed above, the following ADRs have been reported with intrathecal use: Chemical meningitis and meningism at an unknown frequency.
In addition to the ADRs listed above, the following ADRs have been reported with use for ERCP: Elevation of pancreatic enzyme levels and pancreatitis at an unknown frequency.
The majority of the reactions after myelography or use in body cavities occur some hours after the administration.

Description of selected adverse reactions

Based on experience with other non-ionic contrast media, the following undesirable effects may occur with intrathecal use in addition to the undesirable effects listed above:

Psychosis, neuralgia, paraplegia, aseptic meningitis, back pain, pain in extremities, micturition disorder, EEG Abnormal.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

- Intravascular overdose

Symptoms may include fluid and electrolyte imbalance, renal failure, cardiovascular and pulmonary complications.
In case of inadvertent intravascular overdosage, it is recommended to monitor fluids, electrolytes, and renal function.
Treatment of overdose should be directed towards the support of vital functions.

Ultravist is dialyzable (see section ‘Pharmacokinetic properties’).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Watersoluble, nephrotropic, low osmolar X-ray contrast media ATC code: V08AB05
The contrast-giving substance in the Ultravist formulations is iopromide, a non-ionic water-soluble derivative of triiodinated isophthalic acid with a molecular weight of 791.12 in which the firmly bound iodine absorbs the X-rays.

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

5.2 Pharmacokinetic properties

- General Information

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

- Absorption and distribution:

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

Protein binding is negligible (about 1%). There is no indication that iopromide crosses the intact blood-brain-barrier. A small amount crossed the placental barrier in animal studies (≤0.3% of the dose were found in rabbit fetuses)

Following administration in the biliary and/or pancreatic duct during Endoscopic Retrograde Cholangiopancreaticography (ERCP), iodinated contrast agents are systemically absorbed and reach peak plasma concentrations between 1 and 4 h post administration. Maximum serum iodine levels following a mean dose of about 7.3 g iodine were about factor 40 lower compared to maximum serum levels reached after respective intravenous doses.

- Metabolism:

Iopromide is not metabolized.

- Elimination:

The terminal elimination half-life of iopromide is approximately 2 hours, irrespective of the dose. In the dose range tested, the mean total clearance of iopromide amounts to 106 ± 12 ml/min and is similar to the renal clearance of 102 ± 15 ml/min. Thus, excretion of iopromide is almost exclusively renal. Only about 2% of the dose administered is excreted via the fecal route within 3 days.
Approximately 60% of the dose is excreted within 3 hours after intravenous administration via urine. In the mean ≥ 93% of dose was recovered within 12 hours. Excretion is essentially complete within 24 hours.
Following administration into the biliary and/or the pancreatic duct for ERCP urinary iodine serum concentrations returned to pre-dose levels within 7 days.

- Linearity/non-linearity

The pharmacokinetic parameters of iopromide in humans change dose proportionally (e.g. C_{max}, AUC) or are dose independent (e.g. Vss, $t_{1/2}$).

- Characteristics in special patient populations:

Elderly population (aged 65 years and above)
Middle-aged patients (49 - 64 years) and elderly patients (65 - 70 years), without significantly impaired renal function, had total plasma clearances between 74 and 114 ml/min (middle aged group, mean 102 ml/min) and between 72 and 110 ml/min (elderly group, mean 89 ml/min), which is only marginally lower than those in young healthy subjects (88 to 138 ml/min, mean 106 ml/min). The individual elimination half-lives were between 1.9 - 2.9 hours and 1.5 - 2.7

hours, respectively. Compared to the range of 1.4 to 2.1 h in young healthy volunteers, terminal half-lives are similar. The minor differences correspond to the physiologically reduced glomerular filtration rate with age.

Paediatric Population
Pharmacokinetics of iopromide have not been investigated in the pediatric population (see section 4.2).

Patients with renal impairment
In patients with impaired renal function, the plasma half-life of iopromide is prolonged according to the reduced glomerular filtration rate.
The plasma clearance was reduced to 49.4 ml/min/1.73 m^2 (CV = 53%) in mildly and moderately impaired patients (80> CL_{CR} >30 ml/min/1.73 m^2) and to 18.1 ml/min/1.73 m^2 (CV = 30%) in severely impaired patients not depending on dialysis (CL_{CR} = 30 – 10 ml/min/1.73 m^2).
The mean terminal half-life is 6.1 hours (CV = 43%) in mildly and moderately impaired patients (80 ≥ CL_{CR} > 30 ml/min/1.73 m^2) and 11.6 hours (CV = 49%) in severely impaired patients not depending on dialysis (CL_{CR} = 30 – 10 ml/min/1.73 m2).
The amount recovered in urine within 6 h post dose was 38% in mildly to moderately impaired patients and 26% in severely impaired patients, compared to more than 83% in healthy volunteers. Within 24 h post dose the recovery was 60% in mildly to moderately and 51% in severely impaired patients, compared to more than 95% in healthy volunteers. Iopromide can be eliminated by hemodialysis. Approximately 60% of the iopromide dose is removed during a 3 hour dialysis.

Patients with hepatic impairment
Elimination is not affected because only about 2% of dose are excreted in faeces.

5.3 Preclinical safety data

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

- **Systemic toxicity:**

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

- **Genotoxic potential, tumorigenicity:**

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

- **Local tolerance and contact-sensitizing potential:**

Local tolerance studies following single as well as repeated intravenous administration and single intraarterial, intramuscular, paravenous, intraperitoneal, intrathecal and conjunctival administration indicated that no or only slight adverse local effects are to be expected in blood vessels, paravenous tissue, subarachnoidal space or on the human mucosa.
Studies into contact-sensitizing effect, gave no indication of a sensitizing potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium calcium edetate
Hydrochloric acid (for pH adjustment)
Trometamol

Water for injection.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Microbiological stability has been demonstrated for up to 10 hours at room temperature.

6.4 Special precautions for storage

Do not store above 30°C. Keep the bottles in the outer carton and protect from X-rays.

6.5 Nature and contents of container

Infusion bottles: Glass type II
Stopper: Stopper type I, chlorobutyl-elastomer

Presentation:
Ultravist 240:
Bottles of 50ml
Cartons contain 10 bottles of 50ml

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

Ultravist should be warmed to body temperature prior to use.
(See also Section 4.2)

- Visual Inspection

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

- 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 18G is recommended for piercing the stopper and drawing up the contrast medium (dedicated withdrawal cannulas with a lateral aperture, e.g. Nocore-Admix cannulas, are particularly suitable).

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

Additional instructions for auto injector/pump

The contrast medium must be administered by means of an automatic injector, or by other approved procedures which

ensure sterility of the contrast medium.

The tube from the injector to the patient (patient's tube) must be replaced after every patient to avoid cross contamination. The connecting tubes and all disposable parts of the injector system must be discarded when the infusion bottle is empty or ten hours after first opening the container. Instructions of the device manufacturer must be followed.

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

7 MARKETING AUTHORISATION HOLDER

Bayer Limited
The Atrium
Blackthorn Road
Dublin 18

8 MARKETING AUTHORISATION NUMBER

PA 1410/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 September 1986

Date of last renewal: 24 September 2006

10 DATE OF REVISION OF THE TEXT

January 2015