SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ultravist® 370

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 769mg of iopromide (equivalent to 370mg iodine).
Excipient with known effect
Sodium calcium edetate: Each ml contains 0.000534 mmol (equivalent to 0.0123mg) of sodium
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Aqueous solution for injection.
Clear, colourless to pale yellow solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only. X-ray contrast medium for computerised tomography, digital subtraction angiography, intravenous urography, venography (phlebography), arteriography, arthrography, hysterosalpingography and fistulography.

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 or 1.3ml/kg Ultravist 240). 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 240:** 1.5-2.5ml/kg body weight
- **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.
- **Retrograde carotid angiography:** 30-40 ml Ultravist 300/inj.

**Thoracic aortography:**

- **Abdominal aortography:** 40-60 ml Ultravist 300/inj.
- **Bifemoral arteriography:** 40-60 ml Ultravist 300/inj.

**Peripheral angiography:**

- **Upper extremities:**
  - **Arteriography:** 8-12 ml Ultravist 300/inj.
  - **Venography:** 50-60 ml Ultravist 240/inj.
  - 15-30 ml Ultravist 300/inj.

- **Lower extremities:**
Arteriography     20-30 ml Ultravist 300/inj.
Venography     50-80 ml Ultravist 240/inj.
30-60 ml Ultravist 300/inj.

**Angiocardiology:**
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).
- **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
Uncontrolled thyrotoxicosis (see section 4.4).

### 4.4 Special warnings and precautions for use
- **Hypersensitivity reactions**
Ultravist can be associated with anaphylactoid / hypersensitivity or other idiosyncratic reactions characterised by cardiovascular, respiratory and cutaneous manifestations. Allergy-like reactions ranging from mild to severe reactions including shock are possible (see also 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 the 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 the 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.

In order to minimise risk if a severe reaction should occur, patients:

- should lie down during Ultravist administration
- must be kept under close observation for 15 minutes following the last injection as the majority of severe reactions occur at this time
- should remain in the hospital environment (but not necessarily the radiology department) for one hour after the last injection, and should be advised to return to the radiology department immediately if any symptoms develop.

- Thyroid dysfunction

Particularly careful risk/benefit judgement is required in patients with known or suspected hyperthyroidism or goitre, as iodinated contrast media may induce hyperthyroidism and thyrotoxic crisis in these patients. Testing of thyroid function prior to Ultravist administration and/or preventive thyrostatic medication may be considered in patients with known or 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 exposure to excess iodine may cause hypothyroidism, possibly requiring treatment.

- Cerebral arteriosclerosis, pulmonary emphysema or poor general health

For patients with cerebral arteriosclerosis, pulmonary emphysema or poor general health, the need for examination with X-ray contrast media merits careful consideration.
• Renal impairment

Contrast media-induced nephrotoxicity, presenting as a transient impairment of renal function, may occur after intravascular administration of Ultravist.

Acute renal failure may occur in rare cases.

Risk factors include, for example:
- pre-existing renal insufficiency
- dehydration
- diabetes mellitus
- multiple myeloma / paraproteinaemia
- 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.

• Hydration

Adequate hydration must be assured before and after intravascular Ultravist administration in order to minimise the risk of contrast-media-induced nephrotoxicity (see also section 4.2, ‘Renal impairment’). This applies especially to patients with multiple myeloma, diabetes mellitus, polyuria, oliguria or hyperuricemia, as well as to newborns, infants, small children and elderly patients. Existing disturbances of the balance of water and electrolytes must be corrected before the administration of Ultravist.

• 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.

• CNS disorders

Patients with CNS disorders may be at increased risk of having 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 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.

• 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 \textit{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 catheterisation 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 minimise the length of the procedure so as to minimise the risk of procedure-related thrombosis and embolism.

- Phaeochromocytoma

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

- 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 minimise the state of anxiety in such patients.

- Myelography

Ultravist should not be used in myelography.

- 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.

- Ultravist contains sodium

Ultravist contains less than 1 mmol (23 mg) sodium per dose (based on the average amount given to a 70 kg person), i.e. essentially ‘sodium-free’.

### 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 - ‘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 of delayed reactions to Ultravist.

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

Pregnancy
Adequate and well-controlled studies in pregnant women have not been conducted. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic / foetal development, parturition or postnatal development following diagnostic application of iopromide in humans.

Breast-feeding
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 unlikely (see also section 4.4, ‘thyroid dysfunction’).

4.7 Effects on ability to drive and use machines

There is no known effect on the ability to drive or operate machines. 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

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 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 oedema, pharyngeal oedema, asthma, coma, cerebral infarction, stroke, brain oedema, convulsion, arrhythmia, cardiac arrest, myocardial ischemia, myocardial infarction, cardiac failure, bradycardia, cyanosis, hypotension, shock, dyspnoea, pulmonary oedema, 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. 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.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity / anaphylactoid reactions (Anaphylactoid shock*, respiratory arrest*, bronchospasm*, laryngeal* / pharyngeal* / face oedema, tongue oedema*, laryngeal / pharyngeal spasm*, asthma*, conjunctivitis*, lacrimation*, sneezing, cough, mucosal oedema, rhinitis*, hoarseness*, throat irritation*, urticaria, pruritus, angioedema)</td>
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<tr>
<td>Endocrine disorders</td>
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<td>Thyrotoxic crisis, Thyroid disorder</td>
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<td>Psychiatric disorders</td>
<td></td>
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<td></td>
<td>Anxiety</td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness, Headache, Dysgeusia</td>
<td>Vasovagal reactions, Confusional state, Restlessness, Paraesthesia / hypoaesthesia, Somnolence</td>
<td>Coma*, Cerebral ischaemic Infarction*, Stroke*, Brain oedema*, Convulsion*, Transient cortical blindness*, Loss of consciousness, Agitation, Amnesia, Tremor, Speech disorders, Paresis / paralysis</td>
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<tr>
<td>Eye disorders</td>
<td>Blurred / disturbed vision</td>
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<td></td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
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<td>Hearing disorders</td>
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<tr>
<td>Cardiac disorders</td>
<td>Chest pain / discomfort</td>
<td>Arrhythmia*</td>
<td>Cardiac arrest*, Myocardial ischaemia* Palpitations</td>
<td>Myocardial infarction*, Cardiac failure*, Bradycardia*</td>
</tr>
<tr>
<td>System organ class</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not known</td>
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<tr>
<td>Vascular disorders</td>
<td>Hypertension, Vasodilatation</td>
<td>Hypotension*</td>
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<td>Tachycardia, Cyanosis*</td>
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<tr>
<td>Respiratory, thoracic and mediastinal</td>
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<td></td>
<td>Shock*, Thromboembolic events*, Vasospasm*</td>
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<tr>
<td>disorders</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting, Nausea</td>
<td>Abdominal pain</td>
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<td>Dysphagia, Salivary gland enlargement, Diarrhoea</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<tr>
<td>Musculoskeletal, connective tissue and</td>
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<tr>
<td>bone disorders</td>
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<tr>
<td>Renal and urinary disorders</td>
<td></td>
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<tr>
<td>General disorders and administration</td>
<td>Pain, Injection site reactions (various kinds, e.g. pain, warmth*, oedema*, inflammation* and soft tissue injury* in case of extravasation), Feeling hot</td>
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<tr>
<td>site conditions</td>
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<td>Investigations</td>
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</tbody>
</table>

*life threatening and / or fatal cases have been reported

\( ^a \) intravascular use only

\(^i\) identified only during post-marketing surveillance (frequency not known)

**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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

### 4.9 Overdose
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Water soluble, nephrotropic, low-osmolar X-ray contrast media
ATC code: V08AB05

Ultravist (iopromide) is a non-ionic contrast medium for intravascular radiological examinations and has only minimal pharmacological activity within the body.

The rate of protein binding is low and iopromide is a weak liberator of histamine. Cardiovascular and renal tolerance are good.

Ultravist has low osmolality.

The physico-chemical characteristics of the Ultravist range are listed below:

<table>
<thead>
<tr>
<th>Iodine concentration (mg/ml)</th>
<th>150</th>
<th>240</th>
<th>300</th>
<th>370</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality (osm/kg H$_2$O) at 37 °C</td>
<td>0.33</td>
<td>0.48</td>
<td>0.59</td>
<td>0.77</td>
</tr>
<tr>
<td>Viscosity (mPa-s) at 20 °C</td>
<td>2.3</td>
<td>4.9</td>
<td>8.9</td>
<td>22.0</td>
</tr>
<tr>
<td>at 37 °C</td>
<td>1.5</td>
<td>2.8</td>
<td>4.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Density (g/ml) at 20 °C</td>
<td>1.164</td>
<td>1.263</td>
<td>1.328</td>
<td>1.409</td>
</tr>
<tr>
<td>at 37 °C</td>
<td>1.158</td>
<td>1.255</td>
<td>1.322</td>
<td>1.399</td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties

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

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

Protein binding is negligible (about 1 %). There is no indication that iopromide crossed the intact blood-brain barrier. A small amount crossed the placental barrier in animal studies (<0.3% of the dose was found in rabbit foetuses).
Iopromide is not metabolised.

The terminal elimination half-life of iopromide is approximately 2 hours, irrespective of the size of the dose.
In the dose range tested, the mean total clearance of iopromide amounts to 106 ± 12ml/min and is similar to the renal clearance of 102 ± 15ml/min. Thus, excretion of iopromide is almost exclusively renal. Only about 2% of the dose administered is excreted via the faecal 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. The pharmacokinetic parameters of iopromide in humans change dose proportionally (e.g. C_{\text{max}}, \text{AUC}) or are dose independent (e.g. V_{\text{ss}}, t_{1/2}).

Paediatric population:
There are no clinical pharmacokinetic data available for iopromide in paediatric population.

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 mean terminal half-life is 6.1 hours in mildly and moderately impaired patients and 11.6 hours in severely impaired patients not depending on dialysis. Iopromide can be eliminated by haemodialysis. Approximately 60% of the iopromide dose is removed during 3 hours of dialysis.

Patients with hepatic impairment:
Elimination is not affected by impaired liver function.

5.3 Preclinical safety data

There are no pre-clinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium calcium edetate, trometamol, hydrochloric acid (diluted 10%), water for injections.

6.2 Incompatibilities

Some radiologists give an antihistamine or a corticosteroid prophylactically to patients with a history of allergy.

Because of possible precipitation, X-ray contrast media and prophylactic agents must not be injected as mixed solutions.
6.3   Shelf life

3 years

6.4   Special precautions for storage
Store below 30°C. Protect from light and X-rays.

6.5   Nature and contents of container

Colourless glass infusion bottles of 50, 100 and 200 ml. Packs of 10 x 50 bottles and 1 x 100 or 200ml bottles.

Not all pack sizes may be marketed.

6.6   Special precautions for disposal and other handling

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, crystallization (milky-cloudy appearance and/or sediment at the bottom, or floating crystals) may occur very rarely.

The contrast medium solution should not be drawn up into the syringe of the infusion bottle attached to the infusion set until immediately before the examination.

Contrast medium solution not used in one examination session must be discarded.

7   MARKETING AUTHORISATION HOLDER

Bayer plc
Bayer House
Strawberry Hill
Newbury
Berkshire RG14 1JA
United Kingdom

8   MARKETING AUTHORISATION NUMBER(S)
PL 00010/0567
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/04/2004

10 DATE OF REVISION OF THE TEXT

27/03/2017