Ultravist® 300

PROFESSIONAL DATASHEET

1. NAME OF THE MEDICINAL PRODUCT

Ultravist 300, 300mg iodine/mL, solution for injection or infusion
Iopromide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL solution for injection or infusion contains:
623 mg iopromide (equivalent to 300 mg bound iodine).
For the full list of excipients, see section 6.1.

Ultravist 300	Iopromide	Iodine
Concentration (mg/mL)	623	300
Content (g) in Vial containing 10 mL	 6.2	 3.0
Bottle containing 50 mL 75 mL 100 mL 150 mL 200 mL 500 mL	 31.2 46.8 62.3 93.5 124.6 311.5	 15.0 22.5 30.0 45.0 60.0 150.0
Prefilled plastic cartridge containing 75 mL 100 mL 125 mL 150 mL	 46.8 62.3 77.9 93.5	 22.5 30.0 37.5 45.0

3. PHARMACEUTICAL FORM

Ultravist 300: solution for injection or infusion
Clear, colourless to pale yellowish, particle-free solution.
Physico-chemical and physical properties:

Ultravist 300		
pH		6.5 - 8.0
Viscosity (mPa.s or cP)		
at 20 °C		8.9
at 37 °C		4.7
Osmotic pressure at 37 °C		
(MPa)		1.59
(atm)		15.7
Osmolality at 37 °C	(Osm/kg H_2O)	0.59
Osmolarity at 37 °C	(Osm/l sol.)	0.43
Density (g/mL)		
at 20 °C		1.328
at 37 °C		1.322
Molecular weight (g/mol)		791.12

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

- Angiography, angiocardiography, digital subtraction angiography
- Contrast enhancement in computerised tomography
- Urography
- Visualization of body cavities
  (Exception: myelography, ventriculography, cisternography)

4.2 Posology and method of administration

General information

The dose needs to be adjusted in accordance with the patient's age, weight, cardiac and renal function, general condition, pertinent clinical question, as well as the employed examination technique and area to be examined.

The physician determines the suitable iodine concentration and required volume on a patient-by-patient basis. An overview of the recommended volumes for the various concentrations of iopromide solutions for each body region to be visualized is provided in tabular form at the end of this section.

The total allowed dose of 1.5 g iodine per kg of body weight should not be exceeded on any given examination day. For Ultravist 300 this corresponds to a volume of 5 mL per kg of body weight.

As a rule, patients receiving contrast media intravascularly should remain in a reclining position during the administration procedure.

Heating the contrast medium prior to application:

Contrast media that are heated to body temperature prior to application are more well tolerated and are easier to inject due to the lower viscosity.

For further important information on handling see section 6.6.

Type of application:

Ultravist 300: for intravascular, intracavitary use.

The information below applies for the following individual application areas

Intravenous urography

It is important to note that when conducting intravenous urography in children, relatively high doses of contrast medium are required due to the poor physiological concentrating ability of the immature nephron of the infantile kidney.

Computerised tomography (CT)

Ultravist 300 should be administered as a rapid intravenous injection, and if possible, via a high pressure injector. When slow scanners are used, to achieve relatively constant blood levels we recommend that half of the dose be administered as a bolus and the remainder of the dose then given within 2-6 minutes, even if a steady peak cannot be maintained. The scan process is to be started after completion of the initial administration phase.

When performing spiral CT, and in particular when using multi-slice techniques, a variety of data are compiled while the patient during the breath-holding phase.

In order to optimize the effect of the intravenous bolus injection in the region under examination (optimal uptake is achieved at different times in the variously, pathologically altered tissues), the use of an automatic high-pressure injector and bolus is recommended.

When performing CT, the required quantity of contrast medium and administration rate are determined in relation to the organs to be examined, the diagnostic question at hand, but also in consideration of the apparatus actually available for the specific examination (e.g. scan and image forming times). Infusion is recommended when using slow-working devices, and bolus injection for fast scanners.

Digital subtraction angiography (DSA)

In many cases, intra-arterial DSA is able to produce strongly enhanced images of the great vessels and arteries of the neck, kidney and limbs, even in cases where the applied concentration of iopromide solution (Ultravist 300 or 370) would be insufficient for conventional angiography. This method is thus recommended for patients with impaired renal function. When performing arteriography of the lower extremities, in certain cases it may be necessary to apply higher quantities of contrast media (ca. 200 mL), e.g. when both legs need to be examined (see table).

Visualization of body cavities

The contrast medium should be injected under fluoroscopic monitoring when administered in the context of arthrography, hysterosalpingography and ERCP (endoscopic retrograde cholangiopancreatography).

Additional information regarding special patient groups

Neonates and babies

Babies under the age of one year - particularly neonates - are susceptible to an electrolyte imbalance and haemodynamic changes. Caution is therefore required in selecting the dose of contrast medium, conducting the examination, in addition to considering the specific health status of the patient.

Patients with impaired renal function:

Since iopromide is nearly exclusively excreted via the kidneys in unchanged form, it takes longer for iopromide to be eliminated from patients with impaired renal function. In order to reduce the risk of contrast-medium-induced kidney injury, patients with pre-existing renal function impairment should receive the lowest possible dose of contrast medium (cf. sections 4.4 and 5.2). For such patients, it is also recommended to monitor renal function for at least three days after the examination.

Table: Overview of the areas of application of various concentrations of iopromide solutions in X-ray diagnostics given via injection or infusion, the recommended solutions are shown in bold print:

Area of application		Concentration of bound iodine (mg/mL)	Volume (mL)	
			Conventional film-angiography	Digital subtraction angiography
Cerebral angiography				
Aortic arch		**300**	50 - 80	25 - 40
		370	40 - 60	25 - 30
A. carotis communis		**300**	10 - 12	6 - 8
A. carotis externa		**300**	4 - 8	4 - 6
A. vertebralis		**300**	4 - 8	4 - 6
Thoracic angiography				
Aorta		**300**	50 - 70	30 - 50
		370	50 - 60	25 - 30
Abdominal angiography				
Aorta		**300**	50 - 80	25 - 35
		370	40 - 60	20 - 25
A. coeliaca		**300**	25 - 35	15 - 20
A. mesenterica superior		**300**	30 - 40	15 - 20
A. mesenterica inferior		**300**	15 - 25	8 - 12
A. splenica		**300**	15 - 30	8 - 15
A. hepatica		**300**	20 - 40	10 - 20
A. renalis		**300**	8 - 15	5 - 8
Angiography of the extremities				
Upper extremities				
Arteriography		**150**	-	10 - 40
		300	20 - 30	10 - 15
Phlebography		**240**	30 - 40	10 - 15
		300	20 - 30	8 - 15
Visualization of dialysis shunt		**150**	3 - 50	3 - 50
Lower extremities				
Pelvis-leg arteriography		**150**	-	~ 100
		300	70 - 150	40 - 80
		370	60 - 120	40 - 70
A. femoralis		**300**	20 - 30	10 - 15
Phlebography		**240**	80 - 100	60 - 80
		300	60 - 80	60 - 80
Angiocardiography				
Ventricles		**370**	40 - 60	20 - 30
A. coronaria sinistra		**370**	6 - 10	4 - 5
A. coronaria dextra		**370**	4 - 8	4 - 5
Computerised tomography				
Head	adults	240/**300/370**	100	
	children	240/**300**	2.0 mL/kg body weight	
Whole-body	adults	240/**300/370**	100 - 150	
	children	240/**300**	1.0 - 3.0 mL/kg body weight	
Intravenous urography				
Adults		240/**300**/370	1 - 1.5 mL/kg body weight	
Neonates	< 5 kg	240/**300**/370	4 mL/kg body weight	
Babies	5 - < 10 kg	240/**300**/370	3 mL/kg body weight	
Small children	10 - < 30 kg	240/**300**/370	2 mL/kg body weight	
School children	> 30 kg	240/**300**/370	1.5 mL/kg body weight	
Body cavities				
Arthrography		**240/300**/370	2 - 15	
Hysterosalpingography		**240/300**/370	10 - 25	
Fistulography		240/**300**/370	1 - 10	
ERCP		**240/300**/370	10 - 30	
Galactography		**240/300**/370	1 - 3	
Oesophagus-stomach-intestines		**300/370**	10 - 100	
Ureterography, retrograde urography, urethrography, pyelography		**240/300**/370	2 - 20	
Micturitional cystography		**240/300**/370	250 - 500	

4.3 Contraindications

Hypersensitivity (allergy) to the active substance or iodine or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For all types of administration

Allergoid or anaphylactoid reactions (hypersensitivity reactions)

After administration of Ultravist, dose-independent pseudo-allergic (allergoid)/ hypersensitivity reactions or other idiosyncratic reactions (cardiovascular, respiratory and cutaneous reactions) reactions can occur. Pseudo-allergic reactions in varying severities and even shock are possible (also see section 4.8). Most of these reactions occur within one half hour of contrast media administration, but delayed reactions are also possible (after hours or days).

The risk of hypersensitivity reactions increases in case of:

- history of reaction to contrast media
- known bronchial asthma or other predisposition to allergies

At the beginning of every contrast media examination, patients should thus be extensively queried about their medical histories in terms of the abovementioned risk factors. The indication must be determined within strict boundaries for patients with allergic diathesis, due to the greater risk of hypersensitivity reactions (including severe reactions). Due to their irregular occurrence, such events are not predictable in specific cases. Patients treated with beta-blockers may experience stronger hypersensitivity reactions, particularly when bronchial asthma is involved.

Furthermore, patients who experience hypersensitivity reactions who are also taking beta-blockers may be refractory to standard treatment with beta agonists.

Patients with cardiovascular diseases who experience a severe hypersensitivity reaction are at a higher risk for serious or even fatal outcomes. In such cases, i.e. patients with an increased risk for allergic reactions, patients who have already experienced moderate to severe acute reactions, patients with asthma or allergies requiring medicinal treatment - the advisability of pre-medication with corticoids should be considered prior to the contrast media examination.

Preparing for an emergency situation

Irrespective of the quantity and type of administration, even mild allergic symptoms may be the first signs of a serious anaphylactoid reaction requiring treatment. For this reason, iodinated contrast media should only be employed in medical environments where emergency treatment is available, i.e. the necessary equipment and medications, physicians with sufficient clinical experience, as well as trained assisting medical staff. It must therefore be possible to initiate immediate emergency measures for all patients in order to treat a serious reaction, and to maintain direct access to the requisite emergency drugs and emergency surgical kit. The patient should be observed for at least ½ hour after the end of administration, as experience shows that the majority of all serious incidents occur within this time period.

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 of fatal, exfoliative dermatitis, Stevens-Johnson syndrome (SJS), 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.

Thyroid dysfunction

Iodinated X-ray contrast media influence thyroid function because of the free iodide contained in the solutions, in addition to the additional iodide released within the body after administration due to de-iodination. A particularly careful risk-benefit assessment is required for patients with known or suspected hyperthyroidism or for patients with nodular goitre, because iodated contrast media may induce hyperthyroidism and thyreotoxic crisis in such patients. Thyroid function status must therefore be clarified prior to using Ultravist. Preventative thyreostatic medication can be considered for patients with known or suspected hyperthyroidism.

There have been reports of thyroid function test results indicative of hypothyroidism or transient thyroid suppression after administration of iodinated contrast media in adults and paediatric patients. Prior to use of iodinated contrast media, consideration should be given to the potential risk of hypothyroidism in patients with known or suspected thyroid dysfunction.

Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age

Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media. Among patients 0 to 3 years of age exposed to iodinated contrast media, thyroid dysfunction has been reported in 1% to 15% depending on the age of the patient and the dose of the iodinated contrast agent.

Younger age, very low birth weight, prematurity, and the presence of other conditions, such as, admission to neonatal or pediatric intensive care units, and cardiac conditions are associated with an increased risk. Pediatric patients with cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures, such as catheterization and computed tomography (CT).

Pediatric patients 0 to 3 years of age warrant closer monitoring because an underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. Evaluate thyroid function in all pediatric patients 0 to 3 years of age within 3 weeks following exposure to iodinated contrast media, especially in term and preterm neonates. If thyroid dysfunction is detected, treat and monitor thyroid function as clinically needed.

CNS disorders

Patients with CNS disorders may be at increased risk to have neurological complications in relationship to iopromide administration. Neurological complications are more frequent in cerebral angiography and related 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.

Factors which increase blood-brain barrier permeability facilitate the passage of the contrast medium into cerebral tissue, possibly leading 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 ensured in all patients prior to the intravascular administration of Ultravist. This applies in particular to patients who are at an increased risk of contrast medium-associated acute kidney injury (PC-AKI) (see section 4.4 "Intravascular applications – Acute kidney injury") as well as to patients with polyuria, oliguria, neonates, babies, small children and older patients.

Adequate hydration status can be achieved in most patients by oral fluid administration as needed.

Prophylactic intravenous hydration should be considered, especially in patients at an increased risk of PC-AKI. The decision as to which patients require prophylactic intravenous hydration should be based on recommendations from the most recent and evidence-based clinical guidelines and the individual benefit-risk ratio. This should include consideration of the dose applied (e.g. high dose), route of administration ('first pass' exposure) and renal function (presence of severe renal failure). The presence of concomitant diseases should be considered. In the event of concomitant cardiac disease (e.g. advanced heart failure), prophylactic intravenous hydration may lead to serious cardiac complications (also see sections 4.4 "Intravascular applications - Acute kidney injury", "Intravascular applications - Cardiovascular disease" and section 4.8 "Tabulation of adverse reactions").

Anxiety

Conditions involving over-excitement, anxiety and pain can increase the risk of side effects or contrast-media-related reactions. Care should be taken to minimise any anxiety-promoting conditions.

Pre-testing

Pre-testing for hypersensitivity with a low test dose of contrast medium is not recommended, inasmuch as this approach has no predictive value, and on occasion, has even led to serious, and at times even lethal hypersensitivity reactions.

Intravascular applications

Cardiovascular diseases

Patients with serious cardiovascular diseases or severe coronary heart disease are at a higher risk for clinically relevant haemodynamic changes and arrhythmia.

This applies particularly after intra-coronary, left ventricular and right ventricular administration of contrast media (cf. section 4.8). Patients particularly predisposed to cardiac reactions are those with heart failure, severe coronary heart disease, unstable angina pectoris, heart valve diseases, recent cardiac infarction, with coronary bypasses and patients with pulmonary hypertension. Intravascular injection of Ultravist can cause pulmonary oedema in patients with cardiac insufficiency.

Acute kidney injury

Contrast medium-associated acute kidney injury (PC-AKI) may occur after the intravascular contrast medium administration of Ultravist; this can manifest as a transient impairment of renal function or even acute renal failure in rare instances.

Predisposing factors include: existing renal insufficiency (also see section 4.2 "Additional information regarding special patient groups – Patients with impaired renal function"), dehydration (also see section 4.4 "All types of administration – Hydration", diabetes mellitus, multiple myeloma/paraproteinaemia, high doses of contrast media and/or multiple injections of Ultravist.

Patients with moderately to severely (eGFR 44-30 ml/min/1.73m^2) impaired renal function are at an increased risk of PC-AKI in the event of intra-arterial contrast medium administration and "first-pass" renal exposure (e.g. direct contrast medium administration into the renal artery, thoracic and suprarenal abdominal aorta).

Patients with severely impaired renal function (eGFR <30 ml/min/1.73m^2) are at an increased risk of PC-AKI in the event of intravenous or intra-arterial contrast medium administration with "second-pass" renal exposure (e.g. after injection into the right heart, pulmonary artery, carotid artery, subclavian artery, coronary artery, mesenteric artery or infrarenal arteries) (also see section 4.4 "All types of administration - Hydration").

Intravascular Ultravist can be used in patients without residual renal function who require dialysis, because iodine-containing contrast media can be eliminated via dialysis. Haemodialysis should be conducted immediately after the radiological examination. In case of severe renal failure, any additional severe impairment of the liver can result in seriously delayed excretion of the contrast medium, which may require haemodialysis.

Diabetes mellitus

To avoid lactic acidosis, patients with diabetes mellitus receiving metformin treatment should have their serum creatinine levels measured before receiving an intravascular administration of an iodinated contrast medium (see section 4.5).

Based on the results of the renal function test, the discontinuation of existing metformin therapy should be considered. For *emergency patients* and in case of restricted or unknown renal function, physicians must carefully assess the risks versus the benefits of a contrast-enhanced examination and must take the necessary precautions by: discontinuing metformin therapy, hydrating the patient, monitoring renal function values, serum lactate and pH and closely monitoring the patient for any clinical signs of lactic acidosis.

Thromboembolic events

One property of non-ionic contrast media is their low interference with normal physiological functions. It follows that in vitro, non-ionic contrast media is distinguished by a weaker anticoagulant effect, than is ionic contrast media.

In addition to the contrast medium itself, numerous other factors can contribute to the onset of thromboembolic events. These factors include: the duration of the examination procedure, number of injections, type of catheter/syringe materials, underlying diseases and concomitant medications. This needs to be taken into account in the context of vessel catheterisation to minimise the examination-related risk of embolism and thrombosis. In particular, careful angiographic techniques must be used, the catheter should be flushed frequently with physiological saline solution (if possible with heparin), and the overall duration of the procedure needs to be kept to a minimum.

CNS disorders

Caution should be exercised with respect to intravascular administration in patients with acute cerebral infarction or acute intra-cranial haemorrhage, in patients with diseases that can impair the blood-brain barrier, as well as in patients with cerebral oedema or acute demyelinisation. After contrast medium administration, the incidence of cerebral seizures may increase in patients with intra-cranial tumours, metastases or epilepsy. Neurological symptoms arising from cerebrovascular disorders, intra-cranial tumours or metastases, degenerative or inflammatory processes can be exacerbated by intra-arterial contrast media administration. Intra-arterial contrast media injection can trigger vasospasms and subsequent cerebral ischemic phenomena. Patients with symptomatic cerebrovascular disorders, recent stroke or frequent transient ischaemic attacks are at greater risk of suffering contrast-media-induced neurological complications. It is recommended that anticonvulsive therapy be kept close at hand for emergency use.

Further risk factors

Patients with phaeochromocytoma are at higher risk for developing a hypertensive crisis after intravascular contrast medium administration.

Ultravist may exacerbate the symptoms of myasthenia gravis.

Use in body cavities

For patients with acute pancreatitis and acute cholangitis, ERCP with Ultravist should not be conducted until the risks and benefits are carefully assessed.

The procedure must be postponed until any acute symptoms have subsided (3-4 weeks), unless immediate therapeutic measures such as the removal of an obstructive concrement or stenosis bypass are required.

Information about excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose (based on the average amount for a person weighing 70 kg), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Biguanides (metformin): Biguanides may be eliminated in a delayed fashion in patients suffering from acute renal failure or serious chronic kidney disease, which can subsequently accumulate, thereby possibly causing lactic acidosis.

Because Ultravist use can lead to impaired renal function or can exacerbate a renal function disorder, patients treated with metformin may be at an increased risk for developing lactic acidosis, in particular, patients with a pre-existing renal function disorder (cf. section 4.4 "Intravascular applications – Acute kidney injury"). Depending on renal function test results, the advisability of stopping metformin treatment should be carefully considered.

Interleukin-2: Previous treatment (up to several weeks) with interleukin-2 has been linked to an increased risk for delayed onset of contrast media reactions in association with Ultravist use.

Radioisotopes: Following intravascular administration, iodine-containing contrast media can reduce the ability of thyroid tissue to absorb isotopes. As a consequence, the diagnosing and treatment of impaired thyroid gland function with thyrostatic radioisotopes may be impaired for several weeks after using Ultravist, and even longer in isolated cases.

4.6 Pregnancy and lactation

Pregnancy

Suitable and well controlled studies in pregnant women have not been conducted.

Experimental animal reproduction toxicity studies conducted during pregnancy have not shown any evidence of harmful effects in terms of embryo/foetal development, birth, or postnatal development, following iopromide use in man for diagnostic purposes. In humans, the safety of contrast media administration during pregnancy has not yet been sufficiently demonstrated.

Since exposure to radiation during pregnancy must be avoided as far as possible, the benefits of any X-ray examination - with or without contrast media - must be carefully assessed.

This risk-benefit assessment pertaining to the use of iodinated contrast media must also take the iodine sensitivity of the foetal thyroid into account.

Breastfeeding

The safety of Ultravist in breast-fed infants has not been studied. Only a very small portion of iodinated contrast medium passes into breast milk. No damage to the breast-fed infant is to be expected (cf. section 4.4 "Thyroid dysfunction"). The free iodide contained in the contrast medium solution and the iodide additionally released in the body by way of deiodination accumulates to a higher degree in breast milk. In order to protect the breastfeeding baby from an overexposure to iodide (risk of blocking thyroid hormone synthesis), for safety reasons it is recommended that the breastfeeding of babies of less than 4 months of age be suspended for two days, and that any siphoned milk be discarded.

4.7 Effects on ability to drive and use machines

No studies have been conducted as regards the effects on the ability to drive and to use machinery after using Ultravist.

4.8 Undesirable effects

Summary of safety profile

The overall safety profile of Ultravist is based on data taken from clinical studies involving 3,900 patients prior to market launch, and more than 74,000 patients thereafter, in addition to data obtained from spontaneous reporting and literature sources. The most frequently occurring side effects observed in patients after Ultravist use (≥4%) are headache, nausea and vasodilatation. The most serious side effects observed in patients after Ultravist use are anaphylactoid shock, respiratory arrest, bronchospasm, laryngeal oedema, pharyngeal oedema, asthma, coma, cerebral infarction, stroke, cerebral oedema, cerebral seizures/convulsion, arrhythmia, cardiac arrest, myocardial ischemia, myocardial infarction, heart failure, bradycardia, cyanosis, low blood pressure, shock, dyspnoea, pulmonary oedema, respiratory insufficiency, and aspiration.

Different kinds of side effects may occur in association with the use of iodine-containing contrast media. A differentiation is made between unpredictable pseudo-allergic reactions (cf. section 4.4), and pharmacologically explainable and predictable organotoxic reactions. Pseudo-allergic and organotoxic reactions can occur simultaneously, so that it is not always possible to definitively categorise the specific event.

Tabular presentation of adverse events

Side effects observed after Ultravist use are listed in the table below and are categorised according to system organ class. The most suitable MedDRA term was chosen to describe a certain reaction, its synonyms and related symptoms.

Side effects from clinical studies are classified according to their frequency of occurrence. The frequency of occurrence of undesirable effects is defined according to the following categories: Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Unknown (frequency cannot be estimated on the basis of the available data). Side effects taken from post-marketing reporting and those for which no statement regarding frequency of occurrence can be made are listed under "unknown".

System organ class	Common	Uncommon	Rare	Unknown
Immune system		Hypersensitivity/ anaphy-lactoid reactions (anaphylactoid shock[§) *)], Apnoea[§) *)], Bronchospasm[*)], Laryngeal[*)] / Pharyngeal[*)] / Facial oedema, Tongue oedema[§)], Laryngeal / pharyngeal spasm[§)], Asthma[§) *)], Conjunctivitis[§)], Lacrimation[§)], Sneezing, Coughing, Mucosal oedema, Rhinitis[§)], Hoarseness[§)], Throat irritation[§)], Urticaria, Pruritus, Angioedema)		
Endocrine diseases				Thyrotoxic crisis, Disturbed thyroid function
Psychiatric diseases			Anxiety	
Diseases of the nervous system	Dizziness, Headache, Dysgeusia	Vasovagal reactions, Confusion, Restlessness, Paraesthesia/ hypaesthesia, Somnolence		Coma[*)]. Cerebral ischaemia/ infarction[*)], Stroke[*)], Cerebral oedema[a) *)], Cerebral seizures/ convulsions[*)], Temporary cortical blindness[a)], Unconsciousness, Agitation, Amnesia, Tremor, Speech disorders, Paresis/ paralysis, Contrast encephalopathy
Eye diseases	Blurred vision/ visual disturbance			
Diseases of the ear and labyrinth				Impaired hearing
Heart diseases	Chest pain/ tightness in chest	Arrhythmias[*)]	Cardiac arrest[*)], Myocardial ischaemia[*)], Palpitations	Myocardial infarction [*)], Heart failure [*)], Bradycardia [*)], Tachycardia, Cyanosis[*)]
Vascular diseases	Hypertension, Vasodilatation	Hypotension[*)],		Shock[*)], Thrombo-embolic events[a)], Vasospasm[a)]
Diseases of the airways, chest and mediastinum		Dyspnoea[*)],		Pulmonary oedema[*)], Respiratory insufficiency[*)], Aspiration[*)]
Diseases of the gastro-intestinal tract	Vomiting, Nausea	Abdominal pain		Dysphagia, Swelling of salivary gland, Diarrhoea
Diseases of the skin and subcutis				Skin diseases with blister formation (e.g. Stevens-Johnson or Lyell's syndrome), Exanthema, Erythema, Hyperhidrosis, Acute generalised exanthematous pustulosis, Drug reaction with eosinophilia and systemic symptoms

System organ class	Common	Uncommon	Rare	Unknown
Skeletal musculature, connective tissue and bone disease				Compartment syndrome after extravasation[a)]
Diseases of the kidneys and urinary tract				Renal function disturbance[a)], Acute renal failure[a)]
General diseases and symptoms at the adminis-tration site	Pain, Reaction at injection site (various, e.g. pain, sensation of warmth[§)], oedema[§)], inflammation of[§)] and injury to soft tissue[§)] in case of extravasation), Sensation of heat	Oedema		Malaise, Chills, Paleness
Examinations				Changes in body temperature

*) life-threatening and/or cases involving death have been reported,

a) applies only for intravascular application ,

§) only observed in the context of post-marketing reporting (unknown frequency of occurrence)

Intravascular use

Side effects associated with the intravascular administration of iodinated contrast media are usually mild to moderate and transient in nature.

Nevertheless, serious and isolated life-threatening reactions can occur that require rapid and effective emergency treatment. Reactions to contrast media occur much more frequently and are more severe in the context of intravascular administration, than when administered into body cavities (intra-ductal and intracavitary).

Use in body cavities

Since a small amount of contrast media can enter a blood vessel after intra-ductal or intracavitary administration, allergoid reactions such as those described for intra-vascular administration of contrast medium are also possible in association with intracavitary administration. Symptoms occurring in the context of body cavity imaging can vary according to the examined region and are generally elicited by the employed examination techniques.

Most adverse events occur within a few hours of application in body cavities.

Pain due to volume expansion may be experienced when filling body cavities with contrast media. In addition to the side effects described above, an increase in pancreatic enzymes and onset of pancreatitis, incl. necrotising pancreatitis, have been reported after ERCP examinations. The frequency of occurrence of these side effects is unknown, which may be due to an increase in pressure in the narrow pancreas ducts as a result of overfilling with Ultravist.

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.

To report any side effect(s):

Saudi Arabia:
The National Pharmacovigilance Centre (NPC).
SFDA Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa

Egypt:
Egyptian Pharmaceutical Vigilance Centre
Hotline: 15301
Email: pv.followup@edaegypt.gov.eg
Website: www.edaegypt.gov.eg

Other Countries:
Please contact the relevant competent authority

4.9 Overdose

Symptoms of an overdose can include water /electrolyte imbalance, renal failure, as well as cardiovascular and respiratory complications. The aim of overdose treatment is to maintain all vital functions and to immediately initiate symptomatic therapy as indicated. In the event of an accidental overdose, any possible water and electrolyte imbalance must be monitored, in addition to renal function. Ultravist can be dialysed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: water-soluble, nephrotropic, low osmolar X-ray contrast medium (monomeric non-ionic X-ray contrast medium)

ATC Code: V08A B05

Iopromide, the contrast-enhancing substance in all Ultravist application methods, is a tri-iodinated, non-ionic, water-soluble X-ray contrast medium with a molecular weight of 791.12 g/mol. Its contrasting properties are achieved with iodine that is stably bound in the molecule and which absorbs the X rays.

5.2 Pharmacokinetic properties

Resorption/distribution

After intravenous application, plasma concentrations of iopromide drop rapidly due to distribution in the extracellular space and subsequent elimination.

The total distribution volume under steady state conditions amounts to approx. 16 L, which more or less corresponds to the volume of the extracellular space.

Plasma protein binding is negligible (approx. 1%). There is no evidence that iopromide can penetrate an intact blood brain barrier. Experimental studies in animals have shown that slight quantities of iopromide can pass the placenta barrier (≤ 0.3% of the applied dose in rabbit foetuses).

After application in the bile and/or pancreatic ducts in the context of ERCP examination, iodated contrast media are systematically absorbed and achieve the maximum plasma concentrations within 1 to 4 hours post application.

Maximum iodine concentrations in serum following an average dose of approx. 7.3 g iodine were approx. 40 times lower than maximum serum concentrations after the corresponding intravenous application.

Biotransformation:

Iopromide is not metabolised.

Elimination:

The terminal elimination half-life of iopromide amounts to approx. 2 hours, irrespective of the administered dose. When used within the tested dosage range, the mean total clearance of iopromide is 106 ± 12 mL/min, equivalent to a renal clearance of 102 ± 15mL/min.

It follows that iopromide is excreted nearly exclusively via the kidneys.

Only approx. 2% of the applied dose is excreted with the faeces within 3 days.

In conjunction with intravenous injection, approx. 60% of the dose - and after 12 hours on average ≥ 93% of the dose- is excreted with urine after three hours.

Excretion is more or less complete after a period of 24 hours.

After ERCP use in the bile and/or pancreatic ducts, iodine concentrations in serum returned to their original pre-application values within 7 days.

Linearity/non-linearity

The pharmacokinetic properties of iopromide in humans change in proportion to the dose (e.g. C_{max}, AUC) or are dose-dependent (e.g. V_{ss}, t½).

Particularities in special patient groups

Older patients (65 years and older)

Middle-aged patients (49-64 years) and older patients (65 -70 years), who do not suffer from significant renal impairment exhibited a total plasma clearance of between 74 and 114 mL/min (middle-aged patient group averaged 102 mL/min) and between 72 and 110 mL/min (older patient group averaged 89 mL/min); i.e. only slightly lower values than those obtained for younger healthy persons (88 to 138 mL/min, mean 106 mL/min). The individual elimination half-live values were situated between 1.9 -2.9 h and 1.5 -2.7 h. In comparison with the range 1.4 -2.1 h in young healthy volunteers, the terminal half-life period was similar. The slight differences can be explained by an age-related physiological reduction in the glomerular filtration rate.

Paediatric patients

The pharmacokinetic properties of iopromide have not been examined in a paediatric population (cf. section 4.2).

Patients with renal dysfunction

In patients with impaired renal function, the plasma half-life time of iopromide is prolonged due to the reduced glomerular filtration rate.

In patients with slight to moderate renal impairment (80 ≥ CLCR > 30 mL/min/1.73m^2), plasma clearance dropped to 49.4 mL/min/1.73m^2 (CV = 53%), as well as in patients with serious impairment (CLCR = 30-10 mL/min/1.73 m^2), but not in dialysis-dependent patients, i.e. 18.1 mL/min/1.73 m^2 (CV = 30%).

The mean final half-life time is 6.1 h (CV = 43%) in patients with slight to moderately severe renal function disturbances (80 ≥ CLCR > 30 mL/min/1.73 m^2) and 11.6 h (CV = 49%) in patients with severe renal function impairment.

The quantity found in urine within 6 h of the application amounted to 38% in patients with slight to moderate impairment, and 26% in patients with severely impaired renal function. In contrast, the value for healthy volunteers was 83%.

Within 24 h of applying iopromide, decomposition amounted to 60% in slight to moderately impaired patients and, 51% in severely impaired patients, in contrast to more than 95% in health volunteers. Iopromide can be eliminated by way of haemodialysis. Nearly 60% of the iopromide dose can be removed during a 3-hour dialysis session.

Patients with hepatic dysfunction

Excretion is not restricted in patients with liver function impairment, since iopromide is not metabolised and only 2% of the dose is excreted with the faeces.

5.3 Preclinical safety data

Based on the results of conventional studies of pharmacological safety, toxicity in the context of repeated administration, reproduction and genotoxicity, the available preclinical data do not indicate any particular danger in humans.

Systemic toxicity

The toxicity of iopromide is low. Single and repeated daily intravenous systemic tolerance studies in animals did not raise general concerns about single dose administrations of Ultravist in humans for diagnostic purposes.

Reproduction toxicity, genotoxicity

Investigations with iopromide have shown no evidence of embryotoxic, teratogenic or mutagenic effects.

Local tolerance

Local tolerance studies following single and repeated intravenous administration, as well as single intra-arterial, intra-muscular, paravenous, intraperitoneal, intrathecal and conjunctival individual applications have shown evidence that no, or only slight local adverse effects on blood vessels are to be expected in paravascular tissue, in the subarachnoid space, and in human mucous membranes. Studies examining contact sensitizing effects have shown no evidence of any contact-sensitizing potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium calcium edetate, Hydrochloric acid (to adjust pH), Trometamol, Water for injection

6.2 Incompatibilities

Due to possible incompatibility risks, Ultravist should never be mixed with any other medicinal products.

6.3 Shelf life

3 years

The chemical and physical stability of the ready-to-use preparation (solution for injection or infusion) has been demonstrated at 36- 38° Celsius for a period of 10 hours. From a microbiological point of view, the ready-to-use preparation should be used immediately, unless the method used to open the container ensures that any risk of contamination can be ruled out. If the ready-to-use preparation is not administered immediately, the operator must ensure that the remaining solution is used within the allotted time period and under the appropriate conditions.

6.4 Special precautions for storage

Protect from light and X rays. Store below 30°C. Store Ultravist according to instructions and keep out of the sight and reach of children.

6.5 Nature and contents of container

Vial: colourless, glass type I,
Bottle: colourless, glass type II, Stopper: chlorinated butyl elastomer, Prefilled plastic cartridge: Canister: cycloolefin polymer, colourless, siliconised with silicone oil emulsion, Plunger stoppers and tip closure: polyisoprene, type I, siliconised with silicone oil, Solid core: polycarbonate, Safety closure: polypropylene.

Pack sizes:
10 vials, each containing 10 mL
10 bottles, each containing 50, 75, 100, 150 or 200 mL
8 bottles, each containing 500 mL for injectors
2 x 5 prefilled plastic cartridges, each containing 75, 100, 125 or 150 mL

To ensure proper use of the prefilled plastic cartridges, please note the exact marking on the container.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Ultravist should be heated to body temperature prior to application. Ultravist is supplied as a ready-to-use, clear, colourless to pale yellow solution. The contrast medium should be inspected

visually prior to use. Because Ultravist is a highly concentrated solution, crystallisation may occur in rare cases (milky-turbid appearance and/or bottom sediment or swimming crystals). It is prohibited to use contrast media if severely discoloured, if particles (incl. crystals) are visible, or if the container is damaged.

The contrast medium solution should not be drawn up into the syringe or into the infusion reservoir connected to the infusion device until just prior to starting the examination. The rubber stopper may only be pierced once in order to prevent significant quantities of micro-particles from entering the solution via the stopper.

A long-tip cannula with a maximum diameter of 18 G is recommended for piercing the stopper and for drawing up the contrast medium (special withdrawal cannulas with a side holes, e.g. Nocore-Admix cannulas, are particularly suitable). Contrast media solutions for injection or infusion are meant for one-time use only. Any unused contrast media remaining after the examination procedure must be discarded and appropriately disposed of. If an automatic application system is used to administer a medicinal product, the medicinal product manufacturer must provide evidence of the suitability of any such planned use. The instructions for use of the medicinal products in question must be strictly followed. The use of automatic application systems is prohibited in babies and small children. The following rules apply when using prefilled plastic cartridges: contrast media should always be administered by qualified medical staff and the procedure conducted using the appropriate methods and apparatus. Sterile handling techniques must be strictly followed for all injections involving contrast media. Contrast media must be administered using the appropriate injector. Depending on the cartridge type, the required injector type is clearly marked on the container itself. Any pertinent manufacturer instructions must be strictly followed.

7. MANUFACTURER

Bayer AG,
Müllerstrasse 178
13353 Berlin, Germany.

Marketing Authorization Holder:

Bayer AG,
Kaiser-Wilhelm-Allee 1
51368 Leverkusen, Germany.

8. DATE OF REVISION OF THE TEXT

July 2021

9. GENERAL CLASSIFICATION FOR SUPPLY

Prescription-only

This is a medicament

- A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor‘s prescription, the method of use and the instructions of the pharmacist who sold the medicament. The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children.

Council of Arab Health Ministers
Union of Arab Pharmacists

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