הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 3102.50)

תאריך 22.7.2013

שם תכשיר באנגלית ומספר הרישום:

Ultravist 300 (064-18-27492-00)

Ultravist 370 (064-19-27493-00)

שם בעל הרישום _____ Bayer Israel Ltd._____

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות

טקסט חדש	טקסט נוכחי	פרק בעלון
Experience shows that contrast medium is tolerated better if it is warmed to body temperature. Intravenous urography Adults: The minimum dose is 0.8ml/kg body weight Ultravist 370, (1ml/kg Ultravist 300). These doses should provide adequate filling of the ureters. It may be necessary to increase the dose in individual cases. Children: The poor concentrating ability of the immature nephron of infantile kidneys necessitates the use of relatively high doses of contrast medium, i.e. for Ultravist 300: Neonates: 4.0 ml/kg body weight Babies: 3.0 ml/kg body weight Small children: 1.5 ml/kg body weight Computerised tomography Cranial CT: The following dosages are recommended for cranial CT: Ultravist 300: 1-2ml/kg body weight Ultravist 370: 1-1.5ml/kg body weight Whole-body CT: For whole-body computerised tomography, the doses of contrast medium and the rates of administration depend on the organs under investigation, the diagnostic problem and, in particular, the different scan and image-reconstruction times of the scanners in use. Angiography: The dosage depends on the age, weight, cardiac output and general condition of the patient, the clinical problem, examination technique and the nature and volume of the vascular region to be investigated. The following dosages may serve as a guide: Cerebral angiography Aortic arch angiography 50-80 ml Ultravist 300/inj. Selective angiography 6-15 ml Ultravist 300/inj. Retrograde carotid angiography 30-40 ml Ultravist 300/inj.	• Dietary suggestions Normal diet may be maintained up to two hours prior to the examination. During the last two hours the patient should refrain from eating. • Hydration Adequate hydration must be assured before and after intravascular and intrathecal contrast medium administration. This applies especially to patients with multiple myeloma, diabetes mellitus, polyuria, oliguria, hyperuricemia, as well as to newborns, infants, small children and elderly patients. • Newborns (< 1 month) and infants (1 month -2 years) 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. • Anxiety • Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium-related reactions. These patients may be given a sedative. • Warming 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.	**4.2 Posology and method of administration**

Thoracic aortography: 50-80 ml Ultravist 300/inj. 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 . 15-30 ml Ultravist 300/inj. Lower extremities: Arteriography 20-30 ml Ultravist 300/inj. Venography 30-60 ml Ultravist 300/inj. Angiocardiography: Cardiac-ventriculography 40-60 ml Ultravist 370/inj. Coronary angiography: 5-8 ml Ultravist 370/inj. Digital subtraction angiography (DSA): I.V. injection of 30-60 ml Ultravist 300 or 370 as a bolus (flow-rate: 8-12 ml/second into the cubital vein; 10-20 ml/second into the vena cava) is recommended for high-contrast demonstrations of the great vessels, of the pulmonary arteries and of the arteries of the neck, head, kidneys and extremities. Intra-arterial digital subtraction angiography requires smaller volumes and lower iodine concentrations than the intravenous technique. • Paediatric population Young infants (age < 1 year) and especially newborns are susceptible to electrolyte imbalance and haemodynamic alterations. Care should be taken regarding the dose of contrast medium to be given, the technical performance of the radiological procedure and the patient status (see section 5.2). • Patients with renal impairment Since iopromide is excreted almost exclusively in an unchanged form via the kidneys, the elimination of iopromide is prolonged in patients with renal impairment. In order to reduce the risk of additional contrast media-induced renal impairment in patients with pre-existing renal impairment, the minimum possible dose should be used in these patients (see also sections 4.4, 5.1 and 5.2).	Using an incubator, only the calculated number of bottles needed for the examination day should be warmed up to 37°C. If protected from daylight, longer periods of warming have shown no change in chemical purity. However, three months must not be exceeded. • 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. • 4.2.2 Dosage for intravascular use • Intravascular administration of contrast media should, if possible, be done with the patient lying down. • 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 for at least 3 days following the examination. • Dosage should be adapted to age, weight, clinical question and examination technique. • 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. • Between separate injections the body should be given enough time for the influx of interstitial fluid to normalize the increased serum osmolality. If it is necessary in particular instances to exceed a total dose of 300 to 350 ml in the adult, additional water and possibly electrolytes should be given.	

• 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). ~~• Dietary suggestions~~ ~~Normal diet may be maintained up to two hours prior to the examination. During the last two hours the patient should refrain from eating.~~ ~~• Hydration~~ ~~Adequate hydration must be assured before and after intravascular and intrathecal contrast medium administration. This applies especially to patients with multiple myeloma, diabetes mellitus, polyuria, oliguria, hyperuricemia, as well as to newborns, infants, small children and elderly patients.~~ ~~• Newborns (< 1 month) and infants (1 month -2 years)~~ ~~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.~~ ~~• Anxiety~~ ~~Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium-related reactions. These patients may be given a sedative.~~ ~~• Warming 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. Using an incubator, only the calculated number of bottles needed for the examination day should be warmed up to 37°C. If protected from daylight, longer periods of warming have shown no change in chemical purity. However, three months must not be exceeded.~~ ~~• 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.~~ ~~Dosage for intravascular use~~ ~~Intravascular administration of contrast media should, if possible, be done with the patient~~	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 8 - 12 ml Ultravist 300 Lower extremities 20 - 30 ml Ultravist 300 Angiocardiography: Cardiac ventricles 40 - 60 ml Ultravist 370 Intracoronary 5 - 8 ml Ultravist 370 Venography: Upper extremities 15 - 30 ml Ultravist 300 Lower extremities 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 trunc. 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 The dosages and concentrations used in conventional angiography 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	

~~lying down.~~ ~~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 for at least 3 days following the examination.~~ ~~Dosage should be adapted to age, weight, clinical question and examination technique.~~ ~~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.~~ ~~Between separate injections the body should be given enough time for the influx of interstitial fluid to normalize the increased serum osmolality. If it is necessary in particular instances to exceed a total dose of 300 to 350 ml in the adult, additional water and possibly electrolytes should be given.~~ ~~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 8 - 12 ml Ultravist 300~~ ~~Lower extremities 20 - 30 ml Ultravist 300~~ ~~Angiocardiography:~~ ~~Cardiac ventricles 40 - 60 ml Ultravist 370~~ ~~Intracoronary 5 - 8 ml Ultravist 370~~ ~~Venography:~~ ~~Upper extremities 15 - 30 ml Ultravist 300~~ ~~Lower extremities 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.~~	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 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 1.2 g I/kg BW = 4.0 ml/kg BW Ultravist 300 (<1 month) = 3.2 ml/kg BW Ultravist 370 Infants 1.0 g I/kg BW = 3.0 ml/kg BW Ultravist 300 (1 month-2 years) = 2.7 ml/kg BW Ultravist 370 Children 0.5 g I/kg BW = 1.5 ml/kg BW Ultravist 300 (2-11 years) = 1.4 ml/kg BW Ultravist 370 Adolescents 0.3 g I/kg BW = 1.0 ml/kg BW Ultravist 300 and adults = 0.8 ml/kg BW Ultravist 370	

into the cubital vein; 10 - 20 ml/sec. into the vena cava) is only recommended for contrast demonstrations of great vessels of the trunc. 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 The dosages and concentrations used in conventional angiography 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 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 1.2 g I/kg BW = 4.0 ml/kg BW Ultravist 300 (<1 month) = 3.2 ml/kg BW Ultravist 370 Infants 1.0 g I/kg BW = 3.0 ml/kg BW Ultravist 300 (1 month-2 years) = 2.7 ml/kg BW	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, the renal parenchyma is usually highly opacified 3 to 5 minutes and the renal pelvis with the urinary tract 8 to 15 minutes 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,hysterosalpingography and ERCPi 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 - 15 ml Ultravist 300/370 ERCP: Dosage depends generally on clinical question and size of structure to be imaged. Other: Dosage depends generally on clinical question and size of structure to be imaged.	

Ultravist 370 Children 0.5 g I/kg BW = 1.5 ml/kg BW Ultravist 300 (2-11 years) = 1.4 ml/kg BW Ultravist 370 Adolescents 0.3 g I/kg BW = 1.0 ml/kg BW Ultravist 300 and adults = 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, the renal parenchyma is usually highly opacified 3 to 5 minutes and the renal pelvis with the urinary tract 8 to 15 minutes 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. **4.2.3** Dosage for use in body cavities During arthrography,hysterosalpingography and ERCPii 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 - 15 ml Ultravist 300/370 ERCP: Dosage depends generally on clinical qu size of structure to be imaged. Other: Dosage depends generally on clinical qu size of structure to be imaged.		

~~For all indications~~ ~~The following warnings and precautions apply to any mode of administration, however, the risks mentioned are higher in intravascular administration.~~ • Hypersensitivity reactions 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 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. • 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. • 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	For all indications The following warnings and precautions apply to any mode of administration, however, the risks mentioned are higher in intravascular administration. Special Warnings • Hypersensitivity reactions 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. Patients with hypersensitivity or a previous reaction to iodinated contrast media are at increased risk of having a severe reaction. However, such reactions are irregular and unpredictable in nature. • 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 thyreotoxic crisis in these patients. Testing of thyroid function prior to Ultravist administration and/or preventive thyreostatic medication may be considered in patients with known or suspected hyperthyroidism . • The elderly Underlying vascular pathology and neurological disorders often seen in the elderly constitute an increased risk of adverse reactions to iodinated contrast media. • Very poor state of health • The need for examination merits particularly careful consideration in patients with a very poor general state of health. • Special Precautions • For all indications: • Hypersensitivity reactions • Ultravist can be associated with anaphylactoid/ hypersensitivity or other idiosyncratic reactions	**4.4 Special warnings and precautions for use**

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. • Myelography Ultravist should not be used in myelography. ~~• The elderly~~ ~~Underlying vascular pathology and neurological disorders often seen in the elderly constitute an increased risk of adverse reactions to iodinated contrast media.~~ ~~• Very poor state of health~~ ~~The need for examination merits particularly careful consideration in patients with a very poor general state of health.~~ ~~If hypersensitivity reactions occur (see "4 Undesirable effects"), administration of t contrast medium must be discontinu immediately and - if necessary - specific thera instituted via a venous access. It is therefo advisable to use a flexible indwelling cannula intravenous contrast medium administration. permit immediate countermeasures to be taken emergencies, appropriate drugs, an endotrache tube and a respirator should be ready at hand.~~ ~~If premedication is given, a corticosteroid regimen is recommended.~~ ~~**Intravascular use**~~ ~~Adequate hydration should be ensured in all patients who receive Ultravist administration before contrast medium administration, preferably by maintaining intravascular infusion before and after the procedure and until the contrast medium has been cleared by the kidneys.~~ ~~Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, major surgery etc. until the contrast medium has been cleared.~~ ~~Postponing a new contrast medium examination until renal function returns to pre-examination levels.~~ ~~Increased risk of clinically relevant hemodynamic changes and arrhythmia in patients with significant cardiac disease or severe coronary artery disease.~~ ~~In patients with valvular disease and pulmonary hypertension contrast medium administration may lead to pronounced hemodynamic changes. Reactions involving ischemic ECG changes and major arrhythmia are more common in older patients and in those with preexisting cardiac disease.~~	characterized by cardiovascular, respiratory and cutaneous manifestations. • Allergy-like reactions ranging from mild to severe reactions including shock are possible (see "Undesirable effects"). Most of these reactions occur within one hour 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 • Patients who experience such reactions while taking beta blockers may be resistant to treatment effects of beta agonists (see also "Interactions with other medicaments and other forms of interaction"). • In the event of a severe hypersensitivity reaction, patients with cardiovascular disease are more susceptible to serious or even fatal 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. • If hypersensitivity reactions occur (see "4.8 Undesirable effects"), administration of the contrast medium must be discontinued immediately and - if necessary - specific therapy instituted via a venous access. It is therefore advisable to use a flexible indwelling cannula for intravenous contrast medium administration. To permit immediate countermeasures to be taken in emergencies, appropriate drugs, an endotracheal tube and a respirator should be ready at hand. • If premedication is given, a corticosteroid regimen is recommended.	

~~Premedication with alpha-receptor blockers is recommended.~~ ~~• Alcoholism~~ ~~Acute or chronic alcoholism may increase blood-brain barrier permeability. This facilitates the passage of the contrast medium into cerebral tissue, possibly leading to CNS reactions. Caution must also be exercised in alcoholics and drug addicts because of the possibility of a reduced seizure threshold.~~ ~~The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.~~ ~~Caution is advised in patients with homocystinuria because of the risk of inducing thrombosis and embolism.~~ ~~4.4.2 Use in other body cavities~~ ~~The possibility of pregnancy must be excluded before performing hysterosalpingography.~~ ~~Inflammation of the bile ducts or salpinx may increase the risk of reactions following ERCP or hysterosalpingography procedures.~~ ~~Low osmolar water soluble contrast media should be routinely used in gastrointestinal studies in newborns, infants and children because these patients are at particular risk for aspiration, intestinal occlusion or extraluminal leakage into the peritoneal cavity.~~	• 4.4.1 Intravascular use • 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 should be ensured in all patients who receive Ultravist administration before contrast medium administration, preferably by maintaining intravascular infusion before and after the procedure and until the contrast medium has been cleared by the kidneys. • Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, major surgery etc. until the contrast medium has been cleared. • Postponing a new contrast medium examination until renal function returns to pre-examination levels. • Patients on dialysis may receive contrast media for radiological procedures as iodinated contrast media are cleared by the dialysis process. • Cardiovascular disease • Increased risk of clinically relevant hemodynamic changes and arrhythmia in patients with significant cardiac disease or severe coronary artery disease. • In patients with valvular disease and pulmonary hypertension contrast medium administration	

	may lead to pronounced hemodynamic changes. Reactions involving ischemic ECG changes and major arrhythmia are more common in older patients and in those with preexisting cardiac disease. • The intravascular injection of contrast media may precipitate pulmonary edema in patients with heart failure. • CNS disorders • Patients with seizure history or other CNS disorders may be at increased risk to have seizures and neurological complications in relationship to Ultravist administration. Neurological complications are more frequent in cerebral angiography and related procedures. • Pheochromocytoma • Risk of hypertensive crisis • Premedication with alpha-receptor blockers is recommended. • Patients with autoimmune disorders • Cases of severe vasculitis or Stevens-Johnson like syndrome have been reported in patients with preexisting autoimmune disorders. • Myasthenia gravis • The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis. • Alcoholism • Acute or chronic alcoholism may increase blood-brain barrier permeability. This facilitates the passage of the contrast medium into cerebral tissue, possibly leading to CNS reactions. Caution must also be exercised in alcoholics and drug addicts because of the possibility of a reduced seizure threshold. • 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 procedure 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. • The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting. • Caution is advised in patients with homocystinuria because of the risk of inducing thrombosis and embolism. • 4.4.2 Use in other body cavities • The possibility of pregnancy must be excluded before performing hysterosalpingography. • Inflammation of the bile ducts or salpinx may increase the risk of reactions following ERCP or hysterosalpingography procedures. • Low osmolar water-soluble contrast media should be routinely used in gastrointestinal studies in newborns, infants and children because these patients are at particular risk for aspiration, intestinal occlusion or extraluminal leakage into the peritoneal cavity.	
~~As a precaution, biguanides should be stopped 48 hours before until at least 48 hours after contrast medium administration and reinstated only after baseline renal function has been regained).~~ ~~Concomitant use of neuroleptics and antidepressants may reduce the seizure~~	Biguanides (metformin): Transient renal impairment associated with intravascular use of Ultravist can lead to biguanide accumulation and the development of lactic acidosis in patients who are taking biguanides. As a precaution, biguanides should be stopped 48 hours before until at least	**4.5 Interaction with other medicaments and other forms of interaction**

~~threshold, thus increasing the risk of a contrast medium related reaction.~~ ~~Beta-blockers: Patients who experience hypersensitivity reactions while taking a beta blocker may be resistant to treatment effects of beta agonists (see also "Special precautions").~~	48 hours after contrast medium administration and reinstated only after baseline renal function has been regained). Concomitant use of neuroleptics and antidepressants may reduce the seizure threshold, thus increasing the risk of a contrast medium related reaction. Beta-blockers: Patients who experience hypersensitivity reactions while taking a beta blocker may be resistant to treatment effects of beta agonists (see also "Special precautions"). Interleukin-2: Previous treatment (up to several weeks) with Interleukin-2 is associated with an increased risk for delayed reactions to Ultravist.. • Interference with diagnostic tests 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.	
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.~~	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/fetal development, parturition or postnatal development following diagnostic application of iopromide in humans. Lactation: Safety of Ultravist for nursing infants has not been investigated. Contrast media are poorly excreted in human breast milk. Harm to the nursing infant is not likely.	**4.6 pregnancy and lactation**
ראה טבלה- ראי בהמשך וכן התוספת: Summary of the safety profile The overall safety profile of Ultravist is based	הטבלה המחוקה בהמשך, נלקחה מהעלון הקיים. Undesirable effects in association with the use of iodinated contrast media are usually mild to moderate and transient in nature. However, severe and life-	4.8 Undesirable effects

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. המידע שהיה קיים בעלון הנוכחי נמחק. ניתן לראות בטבלה המחוקה בהמשך. ~~Undesirable effects in association with the use of iodinated contrast media are usually mild to moderate and transient in nature. However, severe and life-threatening reactions as well as deaths have been reported. Nausea, vomiting, a sensation of pain and a general feeling of warmth are the most frequently recorded reactions.~~ ~~All indications:~~ ~~Frequency estimates are 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. (Frequency estimations are based predominantly on intravascular use.).~~	threatening reactions as well as deaths have been reported. Nausea, vomiting, a sensation of pain and a general feeling of warmth are the most frequently recorded reactions. Frequency estimates are 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. (Frequency estimations are based predominantly on intravascular use.). ERCP: In addition to the undesirable effects listed above, the following undesirable effects may occur with use for ERCP: Elevation of pancreatic enzyme levels (common), pancreatitis (rare).	

~~ERCP:~~ ~~In addition to the undesirable effects listed above, the following undesirable effects may occur with use for ERCP: Elevation of pancreatic enzyme levels (common), pancreatitis (rare).~~		

טבלה מצורפת הודעה על החמרה (מידע בטיחות) בעלון לרופא

System organ class	Common	Uncommon	Rare	Not known
Immune system disorders		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)		
Endocrine disorders				Thyrotoxic crisis, Thyroid disorder
Psychiatric disorders			Anxiety	
Nervous system disorders	Dizziness, Headache, Dysgeusia	Vasovagal reactions, Confusional state, Restlessness, Paraesthesia / hypoaesthesia, Somnolence		Coma*, Cerebral ischaemia / Infarction*, Stroke*, Brain oedemaa*, Convulsion*, Transient cortical blindnessa, 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*	Cardiac arrest*, Myocardial ischaemia* Palpitations	Myocardial infarction*, Cardiac failure*, Bradycardia*, Tachycardia, Cyanosis*
Vascular disorders	Hypertension Vasodilatation	Hypotension*		Shock*, Thromboembolic eventsa, Vasospasma
Respiratory, thoracic and mediastinal disorders		Dyspnoea*		Pulmonary oedema*, Respiratory insufficiency*, Aspiration*
Gastrointestinal disorders	Vomiting, Nausea	Abdominal pain		Dysphagia, Salivary gland enlargement, Diarrhoea
Skin and subcutaneous tissue disorders				Bullous conditions (e.g. Stevens-Johnson's or Lyell syndrome), Rash, Erythema, Hyperhydrosis
Musculoskeletal, connective tissue and bone disorders				Compartment syndrome in case of extravasationa
Renal and urinary disorders				Renal impairmenta Acute renal failurea
General disorders and administration site conditions	Pain, Injection site reactions (various kinds, e.g. pain, warmth§, oedema§, inflammation§	Oedema		Malaise, Chills, Pallor

	and soft tissue injury§ in case of extravasation), Feeling hot			
Investigations				**Body temperature fluctuations**

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

System organ class	**Common (≥1/100)**	**Uncommon (≥ 1/1,000, <1/100)**	**Rare (< 1/1,000)**
Immunological		Anaphylactoid reactions / hypersensitivity	Anaphylactoid shock (including fatal cases)
Endocrine			Alteration in thyroid function, thyrotoxic crisis
Nervous, Psychiatric		Dizziness, restlessness	Paraesthesia / hypoaesthesia, confusion, anxiety, agitation, amnesia, speech disorders, somnolence, unconciousness, coma, tremor, convulsion, paresis / paralysis, cerebral ischaemia / infarction, stroke. Transient cortical blindness[a]
Eye		Blurred / disturbed vision	Conjunctivitis, lacrimation.
Ear			Hearing disorders.
Cardiac		Arrhythmia	Palpitations, chest pain / tightness, bradycardia, tachycardia, cardiac arrest, heart failure, myocardial ischemia/infarction cyanosis.
Vascular		Vasodilatation	Hypotension, hypertension, shock. Vasospasm,[a] thromboembolic events[a]
Respiratory		Sneezing, coughing	Rhinitis, dyspnea, mucosal swelling, asthma, hoarseness, laryngeal / pharyngeal / tongue / face edema, bronchospasm, laryngeal/pharyngeal spasm, pulmonary edema, respiratory insufficiency, respiratory arrest.
Gastrointestinal	Nausea	Vomiting, taste disturbance	Throat irritation, dysphagia, swelling of salivary glands, abdominal pain, diarrhoea
Skin and subcutaneous tissue		Urticaria, pruritus, rash, erythema	Angioedema, mucocutaneous syndrome (e.g. Stevens-Johnson's or Lyell syndrome)
Renal and urinary		Renal impairment[a]	Acute renal failure[a]
General disorders and administration site conditions	Heat or pain sensations, headache	Malaise, chills, sweating, vasovagal reactions	Pallor, body temperature alterations, edema Local pain, mild warmth and edema, inflammation and tissue injury in case of extravasation

[a] intravascular use only