

Data Sheet

UROGRAFIN®

Solution for Infusion

Sodium Amidotrizoate / Meglumine Amidotrizoate 30% and 76%

Qualitative and Quantitative Composition

1 mL Urografin 30% for infusion contains 0.04 g sodium amidotrizoate and 0.26 g meglumine amidotrizoate (sodium diatrizoate and meglumine diatrizoate) in aqueous solution.

1 mL Urografin 76% contains 0.1 g sodium amidotrizoate and 0.66 g meglumine amidotrizoate (sodium diatrizoate and meglumine diatrizoate) in aqueous solution.

For excipients, see Pharmaceutical Particulars.

Pharmaceutical Form

Solution for injection or infusion.

Clinical Particulars

Therapeutic Indications

Intravenous and retrograde urography.

Also for all angiographic examinations as well as for amniography, arthrography, intraoperative cholangiography, endoscopic retrograde cholangiopancreatography (ERCP), sialography, fistulography, hysterosalpingography, splenoportography, vesiculography and others.

Urografin is not to be used for myelography, ventriculography or cisternography, since it is likely to provoke neurotoxic symptoms in these examinations.

Dosage and Method of Administration

General Information

In the case of abdominal angiography and urography, the diagnostic yield is increased if the bowels are emptied of faecal matter and gas. On the two days prior to the examination patients should therefore avoid flatulent food, in particular peas, beans, lentils, salads, fruit, dark and fresh bread and all kinds of uncooked vegetables. On the day before the examination, patients should refrain from eating after 6 pm. Moreover, it can be appropriate to administer a laxative in the evening. In babies and young children, however, prolonged fasting and the administration of a laxative before the examination are contraindicated.

Adequate hydration must be assured before and after contrast medium administration. This applies especially to patients with multiple myeloma, diabetes mellitus with nephropathy, polyuria, oliguria, hyperuricaemia, as well as to newborns, infants, small children and elderly patients. Disorders of the water and electrolyte balance must be corrected before the examination.

Newborns (< 1 month) and Infants (1 month - 2 years)

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.

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 same 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.

Intravenous Urography

Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least 30 minutes, since experience shows that the majority of all severe incidents occur within this time.

The dosage may vary depending on the age, weight, cardiac output and general condition of the patient.

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.

Between separate injections the body should be given enough time for the influx of interstitial fluid to normalize the increased serum osmolality. To achieve this, a period of 10 - 15 minutes is necessary in adequately hydrated patients. 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.

Injection

Urografin 76% is well suited for intravenous urography.

In general, the rate of injection is 20 mL/minute. If patients with cardiac insufficiency are given 100 mL or more, an injection time of at least 20 - 30 minutes is recommended.

Adults

The dose is 20 mL Urografin 76%. Increasing the Urografin 76% dose to 50 mL considerably increases the diagnostic yield. The dose may be increased yet again if this is considered necessary in special indications.

Children

The physiologically weak concentrating ability of the still immature nephron of infantile kidneys necessitates relatively high doses of Urografin 76%:

up to 1 year	7 - 10 mL
1 - 2 years	10 - 12 mL
2 - 6 years	12 - 15 mL
6 - 12 years	15 - 20 mL
above 12 years	adult dose

Filming Times

The renal parenchyma can be demonstrated best when the film is taken immediately after the end of the administration.

For visualization of the renal pelvis and urinary tract, the first film is taken 3 - 5 and the second 10 - 12 minutes after the administration of the contrast medium. The earlier time should be chosen for younger patients and the later time for older patients.

In newborns, infants and young children it is advisable to take the first film as early as about 2 minutes after the administration of the contrast medium.

Insufficient contrast can necessitate later films.

Infusion

Adults and Adolescents

1 bottle of 100 mL Urografin 76% or 1 bottle of 250 mL Urografin 30% for infusion.

In general, the infusion time should not be less than 5 minutes nor much more than 10 minutes. Infusion times of 20 - 30 minutes are indicated in patients with cardiac insufficiency.

Children

1 bottle of 250 mL Urografin 30% for infusion.

3 - 12 months	6 mL/kg body weight
1 - 8 years	4 mL/kg body weight
Over 8 years	3 mL/kg body weight

Infusion time: 8 - 10 minutes

Compression is contraindicated in babies and is also inadvisable during the infusion of large amounts of contrast medium in children, adolescents and adults, since, if drainage is obstructed, the increased diuresis can lead to rupture of the fornix as a result of the high pressure. Compression may, however, be applied about 10 minutes after the end of the infusion to demarcate organic from functional filling defects.

Filming Times

The first film should be taken towards the end of the infusion. Further films may be taken within the next 20 minutes, or later in case of excretory disturbances.

Retrograde Urography

An approximately 30% solution is generally sufficient for retrograde urography. It is advisable to warm the contrast medium to body temperature to avoid low - temperature stimulus and resultant ureteral spasms.

An Urografin 60% solution may also be used if greater opacification is desirable for special examinations. Signs of irritation are observed extremely rarely despite the high concentration.

Angiography

Urografin is also suitable for angiographic examinations. The 76% solution is preferred for those angiographic examinations which require a particularly high iodine concentration e.g. aortography, angiocardiology, coronary arteriography. 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.

Other Body Cavities

During arthrography, hysterosalpingography and especially ERCP, injections of contrast medium should be monitored by fluoroscopy.

Contraindications

Manifest hyperthyroidism, decompensated cardiac insufficiency.

Hysterosalpingography must not be performed during pregnancy or in the presence of acute inflammatory processes in the pelvic cavity.

ERCP is contraindicated in acute pancreatitis.

Urografin is not to be used for myelography, ventriculography or cisternography, since it is likely to provoke neurotoxic symptoms (pain, convulsions and coma, often with lethal outcome) in these examinations.

Special Warnings and Special Precautions for Use

For All Indications

The following warnings and precautions apply to any mode of administration, however, the risks mentioned are higher in intravascular administration.

Hypersensitivity

Occasionally, allergy - like hypersensitivity reactions have been observed after use of X-ray contrast media such as Urografin (see Undesirable Effects). These reactions are usually manifest as non - serious respiratory or cutaneous symptoms, as mild respiratory distress, reddening of the skin (erythema), urticaria, itching or facial oedema. Serious events such as angioedema, subglottic oedema, bronchospasm and allergic shock are possible. Generally these reactions occur within one hour after administration of contrast media. However, in rare cases delayed reactions may occur (after hours to days).

Patients with hypersensitivity or a previous reaction to iodinated contrast media are at increased risk of having a severe reaction.

Before any contrast medium is injected, the patient should be questioned for a history of allergy (e.g. seafood allergy, hay fever, hives), sensitivity to iodine or to radiographic media and bronchial asthma as the reported incidence of adverse reactions to contrast media is higher in patients with these conditions and premedication with antihistamines and/or glucocorticoids may be considered.

Patients with bronchial asthma are at special risk of having bronchospasms or a hypersensitivity reaction.

Hypersensitivity reactions can be aggravated in patients on beta - blockers, particularly in the presence of bronchial asthma. Moreover, it should be considered that patients on beta - blockers may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.

If hypersensitivity reactions occur (see 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 medicines, an endotracheal tube and a respirator should be ready at hand.

Thyroid Dysfunction

The small amount of free inorganic iodide from iodinated contrast media might interfere with thyroid function. Therefore, the need for examination merits particularly careful consideration in patients with latent hyperthyroidism or goitre.

Cardiovascular Disease

There is an increased risk of severe reactions in individuals with severe cardiac disease and particularly in those with heart failure and coronary artery disease.

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.

Intravascular Use

Renal Failure

Temporary renal failure may occur in rare cases. Preventive measures against acute renal failure following contrast medium administration include:

Identification of high - risk patients e.g. patients with: a history of renal disease, pre - existing renal insufficiency, previous renal failure after contrast medium administration, diabetes mellitus with nephropathy, volume depletion, multiple myeloma, age greater than 60 years, advanced vascular disease, paraproteinemia, severe and chronic hypertension, gout, patients receiving large or repeated doses.

Ensuring adequate hydration in risk patients 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 medicines, 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.

Metformin Therapy

The use of renally excreted intravascular X-ray contrast media can lead to transient impairment of kidney function. This may result in lactic acidosis in patients who are taking biguanides.

As a precaution, biguanides should be stopped 48 hours before until at least 48 hours after contrast medium administration and reinstated only after normal renal function has been regained.

Cardiovascular Disease

In patients with valvular disease and pulmonary hypertension contrast medium administration may lead to pronounced haemodynamic changes. Reactions involving ischaemic ECG changes and major arrhythmia are more common in older patients and in those with pre-existing cardiac disease.

The intravascular injection of contrast media may precipitate pulmonary oedema in patients with heart failure.

CNS Disorders

Particular care should be paid to the intravascular administration of contrast media in patients with acute cerebral infarction, acute intracranial haemorrhage, and other conditions involving blood - brain barrier damage, cerebral oedema or acute demyelination. Intracranial tumours or metastases and a history of epilepsy may increase the incidence of convulsive seizures after administration of iodinated contrast media. Neurological symptoms due to cerebrovascular diseases, intracranial tumours or metastases, degenerative or inflammatory pathologies may be exacerbated by contrast medium administration. Vasospasm and subsequent cerebral ischaemic phenomena may be caused by intraarterial injections of contrast media. Patients with symptomatic cerebrovascular diseases, recent stroke or frequent transient ischaemic attacks have an increased risk of neurological complications.

Severe Liver Dysfunction

In the case of severe renal insufficiency, the coexistence of severe hepatic dysfunction can seriously delay contrast medium excretion, possibly necessitating haemodialysis.

Myeloma and Paraproteinemia

Myeloma or paraproteinemia may predispose to renal impairment following contrast medium administration. Adequate hydration is mandatory.

Pheochromocytoma

Patients with pheochromocytoma may develop a severe (occasionally uncontrollable) hypertensive crisis following intravascular contrast medium use. 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.

Coagulation

Ionic iodinated contrast media inhibit blood coagulation, *in vitro*, more than non - ionic contrast media. Nevertheless medical personnel performing vascular catheterization procedures should consider that 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.

Use in 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 cholangiography, ERCP or hysterosalpingography procedures.

Interaction with Other Medicaments and Other Forms of Interaction

The prevalence of delayed reactions (e.g. fever, rash, flu - like symptoms, joint pain and pruritus) to contrast media is higher in patients who have received interleukin.

Interference with Diagnostic Tests

Following the administration of iodinated contrast media, the capacity of the thyroid tissue to take up radioisotopes for diagnosing disorders of the thyroid is reduced for up to two weeks, and even longer in individual cases.

Pregnancy and Lactation

Reproduction - toxicological studies with meglumine- or sodium amidotrizoate gave no indication of a teratogenic or other embryotoxic potential following an inadvertent administration of Urografin during pregnancy.

It has not been sufficiently demonstrated that 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.

Renally eliminated contrast media like Urografin enter the breast milk in only very small amounts.

Limited data suggest that the risk to the suckling infant of administering salts of diatrizoic acid to its mother is low. Breast-feeding is probably safe.

Effects on Ability to Drive or Use Machines

As with all iodinated contrast media, in rare cases there is a possibility of delayed reactions following contrast medium administration that could impair the ability to drive and use machines.

Undesirable Effects

In order to give an approximate indication of incidence, the following definitions apply when the words "common", "uncommon" and "rare" appear in the text:

common: incidence \geq 1:100

uncommon: incidence $<$ 1:100, but \geq 1:1000

rare: incidence $<$ 1:1000

Intravascular Use

Side effects in association with the use of iodinated intravascular contrast media are usually mild to moderate and transient in nature. However, severe and life-threatening reactions as well as deaths have been reported. The prevalence of adverse reactions in patients receiving ionic contrast media is reported to be over 12% compared to over 3% for nonionics.

Nausea, vomiting, a sensation of pain and a general feeling of warmth are the most frequently recorded reactions.

Anaphylactoid Reactions/Hypersensitivity

Mild angioedema, conjunctivitis, coughing, pruritus, rhinitis, sneezing and urticaria have been reported commonly. These reactions, which can occur irrespective of the amount administered and the mode of administration, may be the first signs of incipient state of shock. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via a venous access (see Special Warnings and Special Precautions for Use).

Severe reactions requiring emergency treatment can occur in the form of a circulatory reaction accompanied by peripheral vasodilatation and subsequent hypotension, reflex tachycardia, dyspnoea, agitation, confusion and cyanosis possibly leading to unconsciousness.

Hypotension, bronchospasm and laryngeal spasm or oedema occur uncommonly.

Delayed contrast medium reactions are rare (see Special Warnings and Special Precautions for Use).

Body as a Whole

Heat sensations and headache have been reported as being common. Malaise, chills or sweating and vasovagal reactions are uncommon.

In rare cases alterations in body temperature and swelling of salivary glands are possible.

Respiratory

Transient disturbance in respiratory rate, dyspnoea and respiratory distress and coughing are common.

Respiratory arrest and pulmonary oedema are rare reactions.

Cardiovascular

Clinically relevant transient disturbance in heart rate, blood pressure, disturbance in cardiac rhythm or function and cardiac arrest are uncommon.

Severe reactions requiring emergency treatment can occur in the form of a circulatory reaction accompanied by peripheral vasodilatation and subsequent hypotension, reflex tachycardia, dyspnoea, agitation, confusion and cyanosis possibly leading to unconsciousness.

Serious thromboembolic events causing myocardial infarction have been reported in rare cases.

Gastrointestinal

Nausea and vomiting are common reactions. Abdominal pain has been reported as being uncommon.

Cerebrovascular

Cerebral angiography and other procedures in which the contrast medium reaches the brain in high concentrations with the arterial blood can be accompanied by transient neurological complications such as: dizziness, headache, agitation or confusion, amnesia, disturbed speech, vision, hearing, convulsions, tremor, paresis/paralysis, photophobia, temporary blindness, coma, and somnolence are uncommon.

Serious, in isolated cases fatal, thromboembolic events causing stroke have been reported on rare occasions.

Renal

In rare cases renal impairment or failure have been reported.

Skin

Mild angioedema, flush reaction with vasodilatation, urticaria, pruritus and erythema have been commonly observed.

Toxic skin reactions such as the mucocutaneous syndrome (e.g. Stevens - Johnson's or Lyell syndrome) may develop in rare cases.

Local Irritation (injection site)

Local pain occurs commonly mainly in peripheral angiography. Extravasation of contrast media including Urografin gives rise to local pain, and oedema, but usually recedes without sequela. However, inflammation and even tissue necrosis have been seen on very rare occasions. Thrombophlebitis and venous thrombosis are uncommon.

Use in Body Cavities

Reactions after the administration into body cavities are rare. The majority of them occur some hours after the administration due to the slow absorption from the area of administration and distribution in the whole organism primarily through diffusion controlled processes.

Some elevation of amylase levels is common following ERCP. Acinar opacification following ERCP has been shown to be associated with an increased

risk of post ERCP pancreatitis. Rare cases of necrotizing pancreatitis have been described.

In connection with hysterosalpingography, cases of vasovagal reactions are uncommon.

Anaphylactoid Reactions/Hypersensitivity

Systemic hypersensitivity is rare, mostly mild and occurs generally in the form of skin reactions. However, the possibility of a severe hypersensitivity reaction cannot be totally excluded. Please refer to the corresponding section on Undesirable Effects in intravascular use for full information on anaphylactoid reactions.

Overdose

In the event of accidental intravascular overdose in humans, the water and electrolyte losses must be compensated by infusion. Renal function needs monitoring for at least the next 3 days.

If needed, haemodialysis can be used to eliminate the bulk of the contrast medium from the patient's system.

Pharmacological Properties

Pharmacodynamic Properties

The contrast - giving substances of Urografin are salts of the amido(dia-)trizoic acid in which the X-ray absorbing iodine is present in stable chemical bond. The physico - chemical characteristics of the injectable solutions of Urografin at the concentrations listed below are:

Urografin	30%	76%
Iodine concentration (mg/mL)	146	370
Osmolality (osm/kg H ₂ O) at 37°C	0.71	2.10
Viscosity (mPa•s) at 20°C	2.2	18.5
at 37°C	1.4	8.9
Density (g/mL) at 20°C	1.164	1.418

Urografin	30%	76%
at 37°C	1.158	1.411
pH-value	6.0 - 7.0	6.0 - 7.0

Pharmacokinetic Properties

Distribution

A concentration corresponding to 2 - 3 g iodine/litre plasma can be expected 5 minutes after an intravenous bolus injection of 1 mL Urografin 60% per kg body weight. Over a period of 3 hours, the blood level falls relatively quickly in the first 30 minutes, then with a half-life of 1 - 2 hours.

Amidotrizoic acid does not penetrate the erythrocytes, it is very quickly distributed in the extracellular space following intravascular administration, but is not able to overcome an intact blood - brain barrier and is transmitted in only minimal amounts into breast milk.

Metabolism and Elimination

At diagnostic doses, amidotrizoic acid undergoes glomerular filtration. About 15% of the dose is eliminated in chemically unchanged form with the urine within 30 minutes after the injection, and more than 50% within 3 hours; no metabolites could be demonstrated.

The kinetics observed on distribution and elimination of Urografin are unrelated to the dose within the clinically relevant range. This means that doubling or halving the dose results in blood levels and an eliminated amount of contrast medium in grams per time unit which are twice or half as high. Because of increased osmotic diuresis at twice the dose, however, the urinary concentration of contrast medium does not increase to the same extent.

Characteristics in Patients

In impaired renal function amidotrizoate can also be eliminated extrarenally via the liver, although at a distinctly reduced rate. Renal contrast media can easily be removed from the body by extracorporeal haemodialysis. Regardless of the site of application, complete elimination within a short period of time is ensured even from tissues.

Preclinical Safety Data

Systemic Toxicity

Results from acute toxicity studies in animals show that there is no risk of acute intoxication following use of Urografin.

Experimental systemic tolerance studies with meglumine- or sodium amidotrizoate following repeated daily intravenous administration produced no findings which object to a single diagnostic administration to humans.

Genotoxic Potential, Tumourigenicity

Studies into genotoxic effects of amidotrizoate *in vivo* and *in vitro* gave no indication of a mutagenic potential.

Tumorigenicity studies have not been carried out.

Due to the absence of genotoxic effects and taking into account the metabolic stability, pharmacokinetics and the absence of indications of toxic effects on fast - growing tissues of amidotrizoate, as well as the fact that Urografin formulations were only administered once, there is no evident risk of a tumourigenic effect on humans.

Local Tolerance and Contact-sensitizing Potential

With the exception of an intramuscular local irritation study (Urografin 76%), animal experimental investigations into local tolerance of Urografin have not been carried out. However, local tolerance studies following paravenous, intraperitoneal and intravenous application as well as application into the oviduct have been carried out with meglumine amidotrizoate. Furthermore, the application sites were examined following repeated intravenous administration of meglumine- or sodium amidotrizoate in the systemic tolerance studies. The results from these studies are to be regarded as representative for Urografin.

These studies gave no indication that adverse local effects are to be expected in blood vessels, on mucous or serous membranes of humans. After inadvertent paravascular administration slight local intolerance reactions could occur.

Animal studies, including the investigation into contact-sensitizing effect, gave no indication of a sensitizing potential of amidotrizoate.

Pharmaceutical Particulars

Presentation

Urografin infusions are clear, colourless to faintly yellowish, aqueous, ionic, hypertonic solutions.

List of Excipients

Sodium calcium edetate
Water for injections

Incompatibilities

Contrast media must not be mixed with any other medicines to avoid the risk of possible incompatibilities.

Special Precautions for Storage

Store at or below 30°C. Protect from light, heat and secondary X-rays.

Store all medicines properly and keep them out of reach of children.

Ultravist can be kept for one day after first opening the container and without withdrawal of any contrast medium.

Nature and Contents of Container

Urografin 30%: Bottles of 250 mL

Urografin 76%: Bottles of 50 mL and 100 mL

Instructions for Use/Handling

Inspection

Urografin is supplied ready to use as a clear, colorless to pale yellow solution.

Contrast media should not be used in case of severe discoloration, the occurrence of particulate matter or defective container.

Handling

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

The rubber stopper should never be pierced more than once to prevent large amounts of microparticles from the stopper getting into the solution. The use of cannulas with a long tip and a maximum diameter of 18 G is recommended for piercing the stopper and drawing up the contrast medium (dedicated withdrawal cannulas with a lateral aperture, e.g. Nococe-Admix cannulas, are particularly suitable).

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

Medicine Classification

General Sales Medicine

Name and Address

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
Auckland 0627

Free phone 0800 233 988

Date of Preparation

17 September 2007

Ref: Urografin Corporate Core Text dated 24 February 2003