PROFESSIONAL INFORMATION: UROGRAFIN 60 % 20 ML and UROGRAFIN 76 % SOLUTION FOR INJECTION

Bayer (Pty) Ltd	**Date of revision of text: 02 September 2018**

SCHEDULING STATUS

S4

PROPRIETARY NAMES AND DOSAGE FORMS

UROGRAFIN 60% 20 ML
UROGRAFIN 76%
Solution for injection

COMPOSITION

UROGRAFIN contains a mixture of sodium amidotrizoate and meglumine amidotrizoate in a proportion of 10:66 in aqueous solution (formed from amidotrizoic acid or diatrizoic acid:3,5-bis-acetamido-2,4,6-triiodobenzoic acid).

UROGRAFIN 60%

1 mL UROGRAFIN 60% contains sodium amidotrizoate 0,08 g and meglumine amidotrizoate 0,52 g. Each 20 mL ampoule contains sodium amidotrizoate 1,60 g and meglumine amidotrizoate 10,40 g (292 mg I/mL).

UROGRAFIN 76%

1 mL UROGRAFIN 76% contains sodium amidotrizoate 0,10 g and meglumine amidotrizoate 0,66 g. Each 20 mL ampoule contains sodium amidotrizoate 2,00 g and meglumine amidotrizoate 13,20 g (370 mg I/mL).
The excipients are sodium calcium edetate and water for injection.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION

A. 28 Contrast media.

PHARMACOLOGICAL ACTION

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 UROGRAFIN are:

	UROGRAFIN 60%	**UROGRAFIN 76%**
Iodine concentration (mg/mL)	292	370
Osmolality (osm/kg H_2O)		
at 37 °C	1,50	2,10
Viscosity (mPa.s)		
at 20 °C	7,2	18,5
at 37 °C	4,0	8,9
Density (g/mL)		

at 20 °C	1,330	1,418
at 37 °C	1,323	1,411
pH value	6,0-7,0	6,0-7,0

Pharmacokinetic properties

Distribution

Plasma protein binding following intravenous injection amounts to less than 10 %.

A concentration corresponding to 2 to 3 g iodine/litre plasma can be expected 5 minutes after an intravenous bolus injection of 1 mL UROGRAFIN 60 %/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 to 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 extra-renally 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.

INDICATIONS

X-ray contrast medium for the delineation of the vascular and renal systems, with the exception of myelography, ventriculography or cisternography since it is likely to provoke neurotoxic symptoms in these examinations.

CONTRAINDICATIONS

Proven or suspected hypersensitivity to iodinated contrast media, uncontrolled thyrotoxicosis, and decompensated cardiac insufficiency.

Hysterosalpingography must not be carried out during pregnancy or in patients with acute inflammatory conditions in the pelvic cavity. Endoscopic retrograde cholangio-pancreatography is contraindicated in acute pancreatitis.

In patients with subarachnoid haemorrhage UROGRAFIN should not be used for cerebral angiography or computerised tomography.

WARNINGS AND SPECIAL PRECAUTIONS

For all indications

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

Hypersensitivity

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.

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

In patients with an allergic disposition, known hypersensitivity to iodinated contrast media or a history of asthma, premedication with antihistamines and/or glucocorticoids may be considered.

Occasionally, allergy-like hypersensitivity reactions have been observed after use of X-ray contrast media such as UROGRAFIN (see Side 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.

Fatal reactions have been associated with the administration of water-soluble contrast media. It is therefore of the utmost importance that a course of action be carefully planned in advance for the treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of a severe reaction. Patients should be observed for a possible severe reaction during and for at least 30 to 60 minutes after administration. In rare cases delayed reactions may occur (after hours to days).

Generally these reactions occur within one hour after administration of contrast media. However, in rare cases delayed reactions may occur (after hours to days).

Hypersensitivity reactions can be aggravated in patients on beta-blockers, particularly in people with 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 Side 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.

Thyroid dysfunction

Particularly careful risk-benefit assessment is required in patients with known or suspected hyperthyroidism or goiter, as iodinated contrast media may interfere with thyroid function, aggravate or induce hyperthyroidism and thyreotoxic crisis.

Testing of thyroid function prior to UROGRAFIN administration and/or preventive thyreostatic medication may be considered in patients with known or suspected hyperthyroidism.

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

In patients with severely restricted renal function, 24 hours are recommended to elapse between two iodinated contrast medium examination sessions.

Patients on dialysis may receive contrast media for radiological procedures as iodinated contrast media are cleared by the dialysis process.

Metformin therapy

The presence of renal damage in diabetic patients is one of the factors predisposing to renal impairment following contrast media administration. This may precipitate lactic acidosis in patients who are taking biguanides.

As a precaution, biguanides should be stopped 48 hours prior to the contrast agent examination and reinstated only after control of 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 intra-arterial injections of contrast media. Patients with symptomatic cerebrovascular disease, 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 paraproteinaemia

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

Phaeochromocytoma

Patients with phaeochromocytoma 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 pre-existing autoimmune disorders.

Myasthenia gravis

The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis and/or precipitate a myasthenic crisis.

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 catheterisation 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 a vascular catheterisation 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 minimise the length of the procedure so as to minimise 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.

Effects on ability to drive and use machines

As with all iodinated contrast media, there is a possibility of delayed reactions following administration in rare cases.

As a precaution, driving or operating machinery should be avoided for the first 24 hours after administration of contrast media.

INTERACTIONS

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.

HUMAN REPRODUCTION

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. Breastfeeding is probably safe.

DOSAGE AND DIRECTIONS FOR USE

General information

Dietary suggestions

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 and 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 newborns, infants and young children, however, prolonged fasting and the administration of a laxative before the examination are contraindicated.

Hydration

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 to 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 units needed for the same examination day should be warmed up to 37 °C.

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 lying down. After the administration, the patient should be observed for at least 30 minutes, since the majority of reactions 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 normalise the increased serum osmolality. To achieve this, a period of 10 to 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.

Recommended dosage for intravenous urography

UROGRAFIN 60% and 76% are equally 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 to 30 minutes is recommended.

Adults

The dose is 20 mL UROGRAFIN 76% or 50 mL UROGRAFIN 60%. 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 to 10 mL.
1 to 2 years	10 to 12 mL.
2 to 6 years	12 to 15 mL.
6 to 12 years	15 to 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 visualisation of the renal pelvis and urinary tract, the first film is taken 3 to 5 and the second 10 to 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.

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, angiocardiography, coronary arteriography. The dosage depends on the clinical problem, examination technique and the nature and volume of the vascular region to be investigated.

Administration into body cavities

Retrograde urography

UROGRAFIN 60% solution may be used for retrograde urography, if greater opacification is desirable for special examinations. Signs of irritation are observed extremely rarely despite the high concentration.

Other body cavities

During arthrography, hysterosalpingography and especially endoscopic retrograde cholangio-pancreaticography injections of contrast medium should be monitored by fluoroscopy.

Handling

The contrast medium solution should not be drawn into the syringe until immediately before the examination.

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

SIDE 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 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 drug reactions in patients receiving ionic contrast media is reported to be over 12 % compared to over 3 % for non-ionics.

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

Anaphylactoid reactions/hypersensitivity

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 an incipient state of shock. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via a venous access (see Warnings and Special Precautions).

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 Warnings and Special Precautions).

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

Local pain occurs commonly mainly in peripheral angiography. Extravasation of contrast media 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

The 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 endoscopic retrograde cholangio-pancreatography. Acinar opacification following endoscopic retrograde cholangio-pancreatography has been shown to be associated with an increased risk of post endoscopic retrograde cholangio-pancreatography pancreatitis. Rare cases of necrotising 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 "Intravascular use" for a full text on anaphylactoid reactions.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

Clear colourless solution, free of particles.

PRESENTATION

Bayer (Pty) Ltd	**Date of revision of text: 02 September 2018**

Colourless glass ampoules each containing 20 ml.

STORAGE INSTRUCTIONS

Store at or below 30 °C in the original packaging. Protect from light, heat and secondary X-rays.
Keep out of reach of children.

REGISTRATION NUMBERS

UROGRAFIN 60% 20 ML	H/28/2843
UROGRAFIN 76%	H/28/2844

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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