Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Urografin 30 %w/v Solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of Urografin 30% for infusion contains 0.04 g sodium amidotrizoate and 0.26 g meglumine amidotrizoate (sodium diatrizoate and meglumine diatrizoate) in aqueous solution, containing the equivalent of 146 mg of Iodine in combined form per ml.

Excipients: Contains 1.45mg (0.063mmol) sodium per ml (Each 250ml bottle contains 362.5mg sodium).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for infusion.
A clear, colourless to faintly yellow, odourless, sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Infusion urography.

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

4.2 Posology and method of administration

General Information

o 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 p. m. 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.

o 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 water and electrolyte balance must be corrected before the examination.

o 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.

o Anxiety

Pronounced states of excitement, anxiety and pain may increase the risk of side effects or intensify contrast medium-related reactions.

o 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.

o 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 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.

Infusion urography

Adults and adolescents
1 bottle of 250 ml Urografin 30 % for infusion.
In general, the infusion 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 newborns and infants 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.

4.3 Contraindications

- Proven or suspected hypersensitivity to iodine-containing contrast media.
- Manifest hyperthyroidism.
- Decompensated cardiac insufficiency.

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.

4.4 Special warnings and precautions for use

The use of contrast media should be carried out under the supervision of trained personnel whose experience qualifies them in the safe conduct of such examinations.

This medicinal product contains 362.50 mg of sodium in each dose (250 mL), equivalent to 18.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

- Hypersensitivity

Occasionally, allergy-like hypersensitivity reactions have been observed after the use of X-ray contrast media such as Urografin (*see 4.8, 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 bronchospasm 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 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.

- Thyroid dysfunction

Particularly careful risk-benefit assessment is required in patients with known or suspected hyperthyroidism or goiter, as iodinated contrast media may interefere 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 neonates, specially 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 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. 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 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.

- 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.

- Cardiovascular disease

In patients with valvular disease and pulmonary hypertension contrast medium administration may lead to pronounced hemodynamic 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 disease, 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.

- 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.

- 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 vascular catheterisation procedures one should be aware of this and pay meticulous attention to the angiographic technique and flush the catheter frequently with physiological saline (if possible with the addition of heparin) and 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.

4.5 Interaction with other medicinal products 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.

Diabetic nephropathy may predispose to renal impairment following intravascular contrast medium 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 medium examination and reinstated only after adequate renal function has been regained.

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.

4.6 Fertility, pregnancy and lactation

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.
Minimal amounts of salts of diatrizoic acid are excreted in human breast milk so harm to the breast-fed infant is not likely.

4.7 Effects on ability to drive and 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.

4.8 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 drug reactions in patients receiving ionic contrast media is reported to be over 12% compared to 3% for nonionics.
Nausea, vomiting, a sensation of pain and a general feeling of warmth are the most frequently recorded reactions.

o 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 section 4.4, Special warnings and precautions for use)*.

Severe reactions requiring emergency treatment can occur in the form of a circulatory reaction accompanied by a 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 section 4.4, Special warnings and precautions for use)*.

o 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.

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

Respiratory arrest and pulmonary oedema are rare reactions.

o Cardiovascular
Clinically relevant transient disturbances 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.

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

o 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.

o Renal
In rare cases renal impairment or failures have been reported.

o 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.

o 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: V08 AA01
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 solution of Urografin at the concentrations listed below are:

Urografin	30%
Iodine concentration (mg/ml)	146
Osmolality (osm/kg H_2O) at 37 °C	0.71
Viscosity (mPa·s) at 20 °C at 37 °C	 2.2 1.4
Density (g/ml) at 20 °C at 37 °C	 1.164 1.158
pH-value	6.0-7.0

5.2 Pharmacokinetic properties

o Distribution

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

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%/kg body weight. Over a period of 3 hours, the blood levels fall 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.

o 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.

o 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.

5.3 Preclinical safety data

o 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.

o Reproduction

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

o Genotoxic potential, tumorigenicity

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 tumorigenic effect on humans.

o 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium calcium edetate
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 5 years.
The product should be used immediately after opening.
Any unused portion should be discarded.

6.4 Special precautions for storage

Do not store above 30^{o}C. Store in the original package to protect from light.
Protect from X-rays.

6.5 Nature and contents of container

Bottle: colourless glass type II
Stopper: stopper type I
chlorobutyl-elastomer
Presentation: Bottles of 250 ml

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The contrast medium solution should not be drawn into the syringe or the infusion bottle attached to the infusion set until immediately before examination.
Vials containing contrast medium solutions are not intended for the withdrawal of multiple doses. The rubber stopper should never be pierced more than once. The use of cannulas with a long tip and a diameter of maximally 18 G is recommended for piercing the stopper and drawing up the contrast medium (dedicated withdrawal cannulas with a side hole, e. g. Nocore-Admix cannulas, are particularly suitable).
Contrast medium solution not used in one examination session must be discarded.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1410/012/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 01 April 1988

Date of last renewal: 01 April 2008

10 DATE OF REVISION OF THE TEXT

November 2022