Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gastrografin, 660mg/ml and 100mg/ml Oral and Rectal Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains Amidotrizoic acid (dihydrate) equivalent to 597.30 mg Amidotrizoic acid (anhydrous), 159.24 mg meglumine and 6.29 mg sodium hydroxide equivalent to 100 mg of sodium amidotrizoate and 660 mg of meglumine amidotrizoate (and containing the equivalent of 370 mg of iodine in combined form per ml).

Excipients: Each ml also contains 3.76mg of sodium or 0.16mmol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral and rectal solution.

Clear, almost colourless, yellowish, aqueous solution with a faint odour of star anise oil.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for use by oral or rectal administration only.

Gastrografin is a contrast medium for the radiological examination of the gastrointestinal tract (also in combination with barium sulphate). It can be administered orally or as an enema and is primarily indicated in cases in which the use of barium sulfate is unsatisfactory, undesirable or contraindicated.

These include suspicion of a radiologically undetectable perforation in the gastrointestinal tract, where acute gastrointestinal haemorrhage exists or is a significant risk, or there is suspected bowel obstruction, or where it is necessary to visualise fistulae of the tract, foreign bodies, or tumours prior to surgery.

For radiological investigation of the gastrointestinal tract in cases in whom perforation or acute gastrointestinal haemorrhage exists or is a significant risk, or there is suspected bowel obstruction, or where it is necessary to visualise fistulae of the tract, foreign bodies, or tumours prior to surgery.

In combination with barium sulphate, Gastrografin has considerably improved routine investigation of the gastrointestinal tract both from a diagnostic and from an organisational point of view – the latter by speeding up the examination. It is unsuitable only for the diagnosis of enteritis.

<u>Further indications:</u>

Treatment of uncomplicated meconium ileus.

Computerised tomography in the abdominal region.

The danger of incorrect diagnoses in computerised tomography in the abdominal region is significantly reduced if the intestine is opacified with Gastrografin, especially for differential diagnoses in the minor pelvis. Gastrografin facilitates delimitation of the intestine from neighbouring organs and permits an assessment of changes in the shape of the pancreas.

4.2 Posology and method of administration

General information

Because of the additives (flavourings and a wetting agent), Gastrografin must not be used intravascularly.

- Dietary suggestions

Prior cleansing of the bowels enhances the diagnostic validity.

- Hydration

Adequate hydration must be ensured 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. Disturbances of water and electrolyte balance must be corrected before the examination.

- Newborns (< 1 month), infants (1 month - 2 years) and children (2 – 11 years)

Young infants (age < 1 year) and especially newborns are susceptible to electrolyte imbalance and haemodynamic alterations. Particular attention should be paid to the dose of contrast medium to be given, the technical performance of the radiological procedure and the patient status. Because of its high osmotic pressure and tendency to absorption from the intestine, Gastrografin should not be administered to newborns, infants and young children in doses higher than those recommended. In newborns and infants low osmolar contrast media can often be used more safely than the high osmolar Gastrografin.

Dosage for oral use

The dosage is dependent on the type of examination and the age of the patient.

Adults and children of 10 years of age and over
Visualisation of the stomach: 60ml

Follow-through examination of the gastrointestinal tract: a maximum of 100ml

In adult patients and children of 10 years of age and over, 60 ml is sufficient for visualisation of the stomach; for a follow-through examination of the gastrointestinal tract a maximum of 100 ml may be required. For elderly and cachectic patients dilution with an equal volume of water is recommended.

For the early diagnosis of a perforation or anastomosis in the oesophagus and/or gastrointestinal tract, the patient should drink up to 100 ml Gastrografin. If the suspected lesion cannot be clearly identified in the X-ray film, a chemical reaction can be employed for further clarification.
After 30 – 60 minutes (later, if the defect is suspected of being in the distal gut), a urine specimen should be taken and 5 ml mixed with 5 drops of concentrated hydrochloric acid. The contrast medium which has undergone renal excretion will appear within 2 hours as a typical crystal formation in the precipitate.

Children
Newborns, infants and young children: 15-30ml (diluted with 3 times its volume of water)

Children (5 to 10 years of age): 15-30ml (can be diluted with twice its volume of water)

In children up to 10 years of age, 15 – 30 ml is generally sufficient. This dose can be diluted with twice its volume of water. For newborns, infants and young children it is recommended that the contrast medium be diluted with 3 times its volume of water.

Computerised tomography (CT)
0.5 - 1.5 l of an approx. 3 % Gastrografin solution (30 ml Gastrografin/1 l water).

Dosage for rectal use

Adults
Up to 500ml Gastrografin dilution (diluted with 3 - 4 times its volume of water)

For adult patients the contrast medium should be diluted with 3 – 4 times its volume of water. In general, unlike a barium-sulphate enema, not more than 500 ml of this Gastrografin dilution is required.

Children
Children (up to 5 years of age): up to 500ml Gastrografin dilution (diluted with 5 times its volume of water)

Children (over 5 years of age): up to 500ml Gastrografin dilution (diluted with 4 - 5 times its volume of water)

For children over 5 years of age, the contrast medium should be diluted with 4 –5 times its volume of water; for younger patients, dilution with 5 times its volume of water is recommended.

Therapy of uncomplicated meconium ileus
Gastrografin can be given by enema for non-operative treatment of an uncomplicated meconium ileus. Advantage is taken of the high osmotic pressure of the contrast medium: the surrounding tissue is forced to release considerable amounts of fluid, which then flows into the gut and dissolves the inspissated meconium.

For the therapy of meconium ileus in the newborn, small amounts of Gastrografin solution diluted 1:3 or more are administered under fluoroscopic control.

Dosage for Gastrografin in combination with barium sulphate

Adults and children of 10 years of age and over
In addition to the usual dose of barium sulphate: 30 ml Gastrografin.

In adult patients and children of 10 years of age and over, addition of approximately 30 ml Gastrografin to the usual dose of barium sulphate has been shown to be most satisfactory.

Children
In addition to the usual dose of barium sulphate:
Children (up to 5 years of age): 2 - 5 ml Gastrografin to 100 ml barium sulphate suspension

Children (from 5 – 10 years of age): 10 ml Gastrografin to 100 ml barium sulphate suspension

In children from 5 – 10 years of age, 10 ml Gastrografin may be added to the required amount of barium sulphate. In patients up to 5 years of age, addition of 2 – 5 ml Gastrografin to 100 ml barium sulphate suspension has proved of value. If necessary (in cases of pylorospasm or pyloric stenosis), the portion of Gastrografin in the suspension may be further increased *(up to 30ml Gastrografin to 100 ml barium sulphate suspension*. This does not affect the contrast.

- Exposures

Exposures of the stomach are taken in the usual way whether Gastrografin is used alone or in combination with barium sulphate.
The time taken for emptying of the stomach is the same as for barium sulphate whereas that for filling of the intestine is shorter. When Gastrografin is used alone, the contrast medium has generally reached the rectum after 2 hours, while the Gastrografin/barium sulphate mixture may take up to 3 hours, or longer in individual cases.
The most favourable time for taking exposures of the colon is indicated by the urge to defaecate which all patients experience.

4.3 Contraindications

Manifest hyperthyroidism.

Hypersensitivity to the active substance or to any of the excipients.

Gastrografin must not be administered undiluted in patients with low plasma volume, as for example in newborns, infants, children and in dehydrated patients, since hypovolaemic complications can be particularly serious in these patients.

Gastrografin must not be administered undiluted in patients with suspected possibility of aspiration or broncho-oesophageal fistula, since hyperosmolarity may cause acute pulmonary oedema, chemical pneumonia, respiratory collapse and death.

4.4 Special warnings and precautions for use

The following risks are higher in the case of intravascular administration of iodinated contrast media but are also relevant for the enteral use of Gastrografin.

• Hypersensitivity
Patients with known hypersensitivity to Gastrografin or any of its ingredients are at increased risk for anaphylactoid/hypersensitivity reactions.

Patients with hypersensitivity or a previous reaction to iodinated contrast media are at increased risk of experiencing a severe reaction. However, such reactions are irregular and unpredictable in nature

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

Patients with bronchial asthma are at particular risk of experiencing bronchospasms or hypersensitivity reactions

As with other contrast agents, Gastrografin can be associated with anaphylactoid/hypersensitivity or other idiosynchratic reactions, characterized by cardiovascular, respiratory or cutaneous manifestations and ranging to severe reactions including shock.

Delayed reactions may occur (hours later or up to several days) (see "Undesirable effects").

Nausea, vomiting, mild angioedema, conjunctivitis, coughing, pruritus, rhinitis, sneezing and urticaria have been reported. 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.

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.

Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are necessary.

The risk of anaphylactoid/hypersensitivity reactions is higher in the case of:

- any history of allergic disorders

- history of bronchial asthma

- a previous anaphylactoid/hypersensitivity reaction to iodinated contrast media.

Particularly careful risk-benefit assessment is required in patients with a previous anaphylactoid/hypersensitivity reaction to any other iodinated contrast medium because of an increased risk of anaphylactoid/hypersensitivity reactions in these patients.

Patients taking beta blockers who experience such reactions may be resistant to treatment with beta agonists.

Patients with cardiovascular disorders are more susceptible to serious or even fatal outcomes of severe anaphylactoid/hypersensitivity reactions.

This medicinal product contains 374 mg of sodium in each bottle (100 ml), equivalent to 18.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

• Thyroid dysfunction
Particularly careful risk-benefit assessment is required in patients with known or suspected hyperthyroidism or goitre, as iodinated contrast media may interfere

with thyroid function, aggravate or induce hyperthyroidism and thyreotoxic crisis.

Testing of thyroid function prior to Gastrografin 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 Gastrografin, either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function, as an exposure to excess idodine may cause hypothyroidism, possibly requiring treatment.

• Very poor state of health
The need for examination merits particularly careful consideration in patients with a very poor general state of health.

• Barium sulphate
If Gastrografin is used together with barium sulphate preparations, attention must be drawn to the contraindications, warnings and possible side effects
relevant to the preparation.

• Gastrointestinal

In case of prolonged retention of Gastrografin in the gastrointestinal tract (e.g. obstruction, stasis), tissue damage, bleeding, bowel necrosis and intestinal perforation may occur.

• Hydration

Adequate hydration and electrolyte balance should be established and maintained in the patients, since the hyperosmolarity of Gastrografin may cause dehydration and electrolyte imbalance.

4.5 Interaction with other medicinal products and other forms of interaction

Hypersensitivity reactions can be aggravated in patients on beta-blockers, particularly in people with bronchial asthma. Patients who experience such reactions while taking beta blockers may be resistant to treatment of anaphylactoid/hypersensitivity reactions with beta agonists.

Interleukin-2: Previous treatment (up to several weeks) with Interleukin-2 is associated with an increased risk of delayed reactions to Gastrografin.

● 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 iodinated contrast agents due to reduced radioisotope uptake.

4.6 Fertility, pregnancy and lactation

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

Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal development (see "Preclinical safety data").

Caution should be exercised when using Gastrografin in pregnant women.

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.

Lactation
No data exist regarding this formulation in lactating women. After intravascular use, salts of the diatrizoic acid are excreted in human breast milk. However, at recommended doses of Gastrografin no effects on the breast-fed child are anticipated. Breast-feeding is probably safe, especially in view of the low enteral absorption of Gastrografin.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

Frequency of adverse reactions from spontaneous reports and literature:

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.

Vomiting, nausea and diarrhoea are the most frequently recorded reactions.

The table below reports adverse reactions by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	Common (≥1/100)	Rare (<1/1,000)	Not Known
Immune system disorders		Anaphylactoid shock Anaphylactoid/hypersensitivity reaction	
Endocrine disorders		Hyperthyroidism	Hypothyroidism
Metabolism and nutrition disorders		Fluid and electrolyte imbalance	
Nervous system disorders		Disturbances in consciousness Headache Dizziness	
Cardiac disorders		Cardiac arrest Tachycardia	
Vascular disorders		Shock Hypotension	
Respiratory, thoracic and mediastinal disorders		Bronchospasm Dyspnoea Medication aspiration Pulmonary oedema following aspiration Aspiration pneumonia	
Gastrointestinal disorders	Vomiting Nausea Diarrhoea	Intestinal perforation Abdominal pain Oral mucosal blistering	
Skin and subcutaneous tissue disorders		Toxic epidermal necrolysis Urticaria Rash Pruritus Erythema Oedema face	
General disorders and administration site conditions		Pyrexia Sweating	

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Immune system disorders, anaphylactoid reaction/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 entirely excluded (see "Special warnings and Precautions for use).

Gastrointestinal disorders:
The hypertonic Gastrografin solution may give rise to diarrhoea, but this ceases as soon as the intestine has been emptied. Existing enteritis or colitis may be temporarily exacerbated. In case of obstruction the prolonged contact with bowel mucosa can lead to erosions and to bowel necrosis.

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

Disorders of water and electrolyte imbalance caused by overdose should be corrected.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The contrast-giving substance of Gastrografin is a salt of the amido(dia-) trizoic acid in which the X-ray absorbing iodine is present in a stable chemical bond.

The physico-chemical characteristics of Gastrografin are listed below:

Iodine concentration (mg/ml)	370
Osmolality (osm/kg H_2O)	
At 37 °C	2.15
Viscosity (mPa·s)	
At 20 °C	18.5
At 37 °C	8.9
Density (g/ml)	
At 20 °C	1.427
At 37 °C	1.417
pH value	6.0 – 7.0

5.2 Pharmacokinetic properties

Absorption of amidotrizoic acid, the radiopaque agent of Gastrografin, following oral administration is only 3 %. Even in the absence of perforation, higher levels of absorption demonstrated by opacification of the renal calyces and ureters, were observed in some patients.

If a perforation of the gastrointestinal tract is present, Gastrografin finds its way into the abdominal cavity or the surrounding tissue, where it is absorbed and finally excreted via the kidneys.

5.3 Preclinical safety data

The taste corrigents saccharin sodium and star anise oil, the solubiliser polysorbate 80 as well as the stabilizing additive disodium edetate contained in Gastrografin are considered to be toxicologically harmless at the doses used. Therefore, risk estimation was only performed for the contrast-giving compounds sodium- and meglumine amidotrizoate.

Non-clinical data reveal no special hazard for humans based on conventional studies of systemic toxicity, genotoxicity, toxicity to reproduction, local tolerance and contact-sensitizing potential.

- Systemic toxicity

Based on the results of preclinical acute toxicity studies, there is no risk of acute intoxication on use of Gastrografin.

Systemic tolerance studies following repeated oral administration have not been carried out and are not considered to be necessary. Only very small amounts of amidotrizoate are systemically available. Systemic tolerance studies with meglumine- or sodium amidotrizoate following repeated daily intravenous administration produced no findings which argue against the single diagnostic intravenous dose generally administered to humans. Under the above-stated circumstances this is all the more true in the case of oral administration.

- Genotoxic potential, tumorigenicity

Studies of genotoxic effects (gene-, chromosomal- and genome mutation tests) using the salt mixture sodium- and meglumine amidotrizoate in vivo and in vitro gave no indication of a mutagenic potential of Gastrografin.

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 any indication of toxic effects of sodium- or meglumine amidotrizoate on fast-growing tissues as well as the fact that Gastrografin is only administered once, there is no evident risk of a tumorigenic effect on humans.

- Toxicity to reproduction

Reproductive-toxicological studies in animals with intravenous administration of meglumine- or sodium amidotrizoate gave no indication of a teratogenic or other embryotoxic potential. Due to the low resorption from the gastrointestinal tract (see systemic tolerance studies) no risk to either the pregnancy or the foetus is to be expected following an inadvertent administration of Gastrografin during pregnancy.

- Local tolerance and contact-sensitizing potential

Local tolerance studies of Gastrografin on the mucous membranes in the gastro-intestinal tract were not performed. However, local tolerance studies following intraperitoneal administration as well as administration into the oviduct using meglumine amidotrizoate gave no indication that adverse local effects on the mucous membranes of the human gastro-intestinal tract are to be expected. This evaluation is supported by many years of clinical experience with Gastrografin.

Studies of contact-sensitizing effect gave no indication of a sensitizing potential of meglumine amidotrizoate. However, many years of clinical experience with Gastrografin show that the anaphylactoid reactions known to appear after other iodine-containing contrast media can occur.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Disodium edetate
Saccharin sodium
Polysorbate 80
Star anise oil
Purified water

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2, Posology and Administration.

6.3 Shelf life

Unopened: 4 years.

Opened: Solution not used within one day after opening the bottle must be discarded.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package to protect from light. Protect from X-rays.

6.5 Nature and contents of container

Bottle of 100 ml.

Bottle: Amber, glass type III Ph. Eur. One bottle per pack.

Pilferproof closure: high density polyethylene, PE-HD, coloured, with sealing disk, low density polyethylene, PE-LD, natural.

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

Contrast medium solution not used within one day after opening the bottle must be discarded.

At temperatures below 7ºC Gastrografin tends to crystallise but this can be reversed by gently warming and shaking the bottle. This phenomenon has no effect on the effectiveness or stability of the preparation.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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