1 NAME OF THE MEDICINAL PRODUCT

XENETIX 250, 300, 350 solution for injection
(250, 300, 350 mg iodine/mL)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION PER 100 mL

Xenetix 250 Xenetix 300 Xenetix 350
Iobitridol ..... 54.8400 g ..... 65.8100 g ..... 76.7800 g
Equivalent to iodine ..... 25.0000 g ..... 30.0000 g ..... 35.0000 g
Excipients: Edetate calcium disodium; Tromethamine hydrochloride
Tromethamine; Hydrochloric acid or sodium hydroxide; Water for injection

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Xenetix 250
For adults and children undergoing:

- phlebography
- chest CT-scan
- intra-arterial digital subtraction angiography

Xenetix 300, 350
For adults and children undergoing:

- intravenous urography
- brain or whole-body CT scan
- intravenous digital subtraction angiography
- arteriography
- angiocardiography

4.2 Dosage and method of administration

Doses will be adjusted as a function of the examination and the regions of interest as well as to body weight, and the renal function of the subject, particularly in children.
The recommended mean doses are as follows:

Xenetix 250

Total volume (min.-max.) mL	Mean dose (mL/kg)	Indications
150-220	2.6	Phlebography
95-170	2.0	Chest CT-scan
75-360	3.1	Intra-arterial digital subtraction angiography

Xenetix 300

Total volume (min.-max.) mL	Mean dose (mL/kg)	Indications
50-100 100	1.2 1.6	Intravenous urography: • fast injection: • slow injection:

20-100 20-150	1.4 1.9	CT-scan • Brain • whole-body
40-270	1.7	Intravenous digital subtraction angiography
42-210 85-300	1.8 2.8	Arteriography • Brain • lower limbs
70-125	1.1	Angiocardiography

Xenetix 350

Total volume (min.-max.) mL	Mean dose (mL/kg)	Indications
50-100	1	Intravenous urography
40-100 90-180	1 1. 8	CT-scan • brain • whole-body
95-250	2.1	Intravenous digital subtraction angiography
105-205 80-190 155-330	2.2 1.8 3.6	Arteriography • peripheral • lower limbs • abdominal
65-270 10-130	1.9 4.6	Angiocardiography • adults • children

4.3 Contra-indications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Xenetix is contraindicated in patients hypersensitive to the product.
A history of sensitivity to iodine contraindicates the use of Xenetix (see Warnings). In the absence of specific studies, iobitridol is not indicated for myelography.

4.4 Special warnings and precautions for use

Warnings

As in the case of all iodinated contrast agents, non-ionic water soluble tri-iodinated products may induce mild, severe or fatal intolerance reactions, often of early onset
but sometimes delayed.
These reactions cannot be predicted but are more frequent in patients with a history of allergy (hives, asthma, hay-fever, eczema, various food and drug allergies) or who
have shown particular sensitivity during a previous examination with an iodinated
contrast medium.

Risk-benefit should be considered when dehydration exists, especially when associated with pre-existing renal or hepatic disease, advanced vascular disease, and diabetes mellitus, in infants, young children and elderly patients.
Screening for these reactions by means of iodine reaction tests or any other tests currently available is not possible.

Precautions for use
During the examination, the following are required:

- surveillance by a physician
- maintenance of an intravenous access for emergency treatment in the event of a reaction.

Caution is required in patients presenting with severe liver or kidney failure.
Water intake need not be restricted. It is advisable to maintain abundant urine output in subjects with kidney failure, diabetes mellitus, myeloma or hyperuricemia and in very young
children and atheromatous subjects.
Premedication is advisable for subjects at a high risk of reaction (allergy, history of poor tolerance to iodinated products).
Given the risk involved, emergency resuscitation equipment must be available, particularly when the subject is concomitantly receiving ß-blockers (see Drug interactions), since adrenaline and plasma expansion have little effect in such cases.

4.5 Drug interactions and other forms of interactions

Combinations requiring special precautions
Diuretics: In the event of dehydration induced by diuretics, there is an increased risk of acute kidney failure, in particular when high doses of iodinated contrast media are administered. The subject should be rehydrated before the iodinated contrast medium is administered.
Metformin: Lactic acidosis was induced by functional kidney failure related to radiological investigation of a subject with diabetes mellitus. Metformin treatment must be withdrawn 48 hours before the examination and only reinstituted 2 days after the examination
Beta-adrenergic blocking agents: Concurrent intravascular administration with beta-adrenergic blocking agents may increase the risk of moderate to severe anaphylactoid reaction; also hypotensive effects may be exacerbated; discontinuation of the beta-adrenergic blocking agent may be advisable before administration of contrast media in patients with other risk factors.

4.6 Pregnancy and Lactation

Pregnancy
The safety of iobitridol administration to pregnant women has not been demonstrated. Animal studies have shown no evidence of teratogenic effects. However, all exposure to X-rays should be avoided during pregnancy. The decision of whether or not to perform the examination should be based on careful evaluation of the expected benefit and potential risk.

Lactation
No clinical studies have been conducted on the secretion of iobitridol in breast-milk. Animal studies have shown excretion in breast-milk to be low (3%).

4.7 Effects on ability to drive and use machines

Not relevant

4.8 .Adverse reactions

Benign reactions may occur: feeling of hotness, very rarely nausea, vomiting and redness of the skin. These reactions are transient and devoid of clinical consequences.
More serious manifestations are possible. Reactions may occur as an isolated disorder or combination of disorders: cutaneous, respiratory, neurosensory, gastrointestinal and cardiovascular disorders. The latter may consist of cardiovascular collapse of variable severity. Exceptionally, shock and/or circulatory arrest may occur.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il /

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Xenetix 250, 300, 350 is a non-ionic water-soluble low-osmolality contrast medium for uroangiography.
The iobitridol molecule exhibits a stable and balanced hydrophilic character.
The evaluation of overall safety with respect to the hemodynamic, cardiovascular, bronchopulmonary, renal, neurological, vascular and rheological systems has shown that the safety profile of iobitridol is the same as that of other non-ionic water-soluble tri-iodinated lowosmolality contrast media, particularly in cardiovascular or neurological terms, or comparable to that of a reference solution.

5.2 Pharmacokinetic properties

Following intravascular injection, iobitridol is distributed through the vascular system and interstitial space. It is rapidly eliminated by the renal route (glomerular filtration without reabsorption or secretion at tubule level) in unchanged form.
In cases of kidney failure, heterotropic excretion occurs via the biliary route. Iobitridol can be dialyzed.

5.3 Preclinical safety data

Toxicological studies using the intravenous route did not show any adverse effects except under conditions far removed from those scheduled for clinical practice (dose level, dose repetition). As is the case for all water-soluble non-ionic tri-iodinated contrast media, high (25- 50 mL/kg) single doses induce transient signs of hypothermia, respiratory depression or dosedependent histological signs in the target- organs (liver, kidney) consisting of hepatocellular vacuolization, vacuolization and tubule ectasia. Repeated administration of high doses (8 mL/kg) to the dog, over 28 days, resulted in granular and vacuolar degeneration that was
reversible on withdrawal of treatment.
Local irritation may be observed in the event of perivascular infiltration.
No evidence of mutagenicity was found under the test conditions used. No evidence of mutagenicity was found in animal studies.

6 PHARMACEUTICAL PROPERTIES **INCOMPATIBILITIES**

6.1 **List of excipients**

Sodium calcium edetate, trometamol hydrochloride, trometamol, hydrochloric acid or sodium hydroxide (for pH adjustment), water for injection.

6.2 Incompatibilities

To prevent the risk of incompatibility, no other medication should be injected in the
same syringe.

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store protected from light at a temperature of less than 30°C.
However, the stability studies have shown that the product may be stored at temperatures of less than 35°C.

7 MANUFACTURER:

Lab. Guerbet, France

8 MARKETING AUTHORISATION NUMBERS:

XENETIX 250 , 105-07-28746

XENETIX 300 , 105-07-28747

XENETIX 350 , 105-07-28748

9 REGISTRATION HOLDER:

Promedico Ltd. Baltimore St. Petach-Tikva

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