

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

XENETIX 250

XENETIX 300

XENETIX 350

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XENETIX 250

Per 100 mL of solution:

lobitridol 54.84 g (548.4 mg/ml)
corresponding quantity of iodine..... 25 g (250 mg/ml)

- Iodine content per mL: 250 mg
- Viscosity at 20 °C : 6 mPa.s
- Viscosity at 37 °C : 4 mPa.s
- Osmolality: 585 mOsm / kg H₂O
- Iodine quantity per 50 mL bottle: 12.5 g
- Iodine quantity per 100 mL bottle: 25 g
- Iodine quantity per 200 mL bottle: 50 g
- Iodine quantity per 500 mL bottle: 125 g

XENETIX 300

Per 100 mL of solution:

lobitridol 65.81 g (658.1 mg/mL)
corresponding quantity of iodine..... 30 g (300 mg/mL)

- Iodine content per mL: 300 mg
- Viscosity at 20°C: 11 mPa.s
- Viscosity at 37°C: 6 mPa.s
- Osmolality: 695 mOsm/kg H₂O
- Iodine quantity per 20 mL bottle: 6 g
- Iodine quantity per 50 mL bottle: 15 g
- Iodine quantity per 60 mL bottle: 18 g
- Iodine quantity per 75 mL bottle: 22.5 g
- Iodine quantity per 100 mL bottle: 30 g
- Iodine quantity per 150 mL bottle: 45 g
- Iodine quantity per 200 mL bottle: 60 g
- Iodine quantity per 500 mL bottle: 150 g

XENETIX 350

Per 100 mL of solution:

lobitridol 76.78 g (767.8 mg/mL)

corresponding quantity of iodine..... 35 g (350 mg/mL)

- Iodine content per mL: 350 mg
- Viscosity at 20°C: 21 mPa.s
- Viscosity at 37°C: 10 mPa.s
- Osmolality: 915 mOsm/kg H₂O
- Iodine quantity per 20 mL bottle: 7 g
- Iodine quantity per 50 mL bottle: 17.5 g
- Iodine quantity per 60 mL bottle: 21 g
- Iodine quantity per 75 mL bottle: 26.25 g
- Iodine quantity per 100 mL bottle: 35 g
- Iodine quantity per 150 mL bottle: 52.5 g
- Iodine quantity per 200 mL bottle: 70 g
- Iodine quantity per 500 mL bottle: 175 g

Excipient with known effect: sodium (up to 3.5 mg per 100 mL).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This medicinal product is for diagnostic use only.

Xenetix 250

Contrast agent to be used for adults and children undergoing:

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

Xenetix 300, Xenetix 350

Contrast agent to be used for adults and children undergoing:

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

4.2. Posology and method of administration

The doses must be adapted to the examination and the areas to be opacified, and to the subject's weight and renal function, particularly in children.

Recommended mean dosages:

Xenetix 250

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

Xenetix 300

Indications	Mean dose mL/kg	Total volume (min-max) mL
Intravenous urography:		
• rapid intravenous injection	1.2	50-100
• slow intravenous injection	1.6	100
• Computed tomography (CT)		
Head	1.4	20-100
• Whole body	1.9	20-150
Digital subtraction angiography by intravenous route	1.7	40-270
Arteriography		
• Cerebral	1.8	42-210
• Legs	2.8	85-300
Angiocardiography	1.1	70-125

Xenetix 350

Indications	Mean dose mL/kg	Total volume (min-max) mL
Intravenous urography	1.0	50-100
• Computed tomography (CT)Head	1.0	40-100
• Whole-body	1.8	90-180
Digital subtraction angiography by intravenous route	2.1	95-250
Arteriography		
• peripheral	2.2	105-205
• legs	1.8	80-190

• abdominal	3.6	155-330
Angiocardiography		
• adults	1.9	65-270
• children	4.6	10-130

Method of administration

XENETIX 250 mg is for use by intravascular route and as a single-dose for the 50, 100, 200 and 500 mL pack sizes.

XENETIX 300 mg is for use by intravascular route and as a single-dose for the 20, 50, 60, 100, 150, 200 and 500 mL pack sizes

XENETIX 350 mg is for use by intravascular route and as a single-dose for the 20, 50, 60, 100, 150, 200 and 500 mL pack sizes.

4.3. Contraindications

- Hypersensitivity to iobitridol or to any of the excipients listed in section 6.1.
- History of a major immediate reaction or delayed cutaneous reaction(see Section 4.4 and 4.8) to a XENETIX injection. In the absence of specific studies, iobitridol is not indicated for myelography.
- Manifest thyrotoxicosis.

4.4. Special warnings and precautions for use

- Regardless of the route of administration and dose, there is a risk of allergy.
- The risk of intolerance is not clear when it comes to medicinal products administered locally for the opacification of body cavities:
 - a) Administration by certain routes (articular, biliary, intrathecal, intrauterine, etc.) leads to fairly significant systemic passage: systemic effects may be observed.
 - b) Oral or rectal administration normally results in very limited systemic diffusion; If the digestive mucosa is normal, no more than 5% of the administered dose is found in the urine, the remainder being eliminated in faeces. However, in the event of damage to the mucosa, absorption is increased; it is total and rapid in the event of perforation, with passage into the peritoneal cavity, and the drug is eliminated in the urine. The potential occurrence of dose-dependent systemic effects is therefore dependent on the condition of the digestive mucosa.
 - c) The immunoallergic mechanism is non-dose-dependent and may be observed in any patient, regardless of the route of administration.

The frequency and intensity of adverse reactions therefore differs between the following two groups:

- Medicinal products administered by the vascular route and certain local routes
- Medicinal products administered by the digestive route and absorbed very little under normal conditions.

4.4.1. General information applicable to all iodinated contrast agents

4.4.1.1 Warnings

In the absence of specific studies, myelography is not an indication for XENETIX.

All iodinated contrast agents may cause minor or major reactions that can be life-threatening. These reactions can occur immediately (within 60 minutes) or be delayed (within 7 days). They are often unpredictable.

The risk of major reactions means that emergency resuscitation equipment must be immediately available.

Several mechanisms have been discussed:

- Direct toxicity to the vascular endothelium and tissue proteins.
- Pharmacological action modifying the concentration of certain endogenous factors (histamine, complement components, inflammatory mediators) is more common with hyperosmolar products.
- XENETIX contrast agent-dependent immediate IgE allergy (anaphylaxis)
- Allergic reactions of cellular mechanism (delayed skin reactions)

Patients who have experienced a reaction with a previous administration of an iodinated contrast agent have an increased risk of a new reaction in the event of re-administration of the same or possibly another iodinated contrast agent and are therefore considered to be at risk.

Iodinated contrast agents and the thyroid (see also Section 4.4.1.2.5.)

Prior to administration of iodinated contrast agent, it is important to ensure that the patient is not due to undergo a scintigraphic or biological examination of the thyroid or receive radioactive iodine for therapeutic purposes.

In fact, the administration of any type of iodinated contrast agents interferes with the hormonal doses and iodine uptake by the thyroid or thyroid cancer metastases until normalization of the ioduria.

Other warnings

Extravasation is a non-exceptional complication (0.04% to 0.9%) of intravenous injections of contrast agents. This occurs more frequently with the high osmolar products, most of the injuries are minor, however severe injuries such as skin ulceration, tissue necrosis, and compartment syndrome may occur with any iodinated contrast medium. The risk and/or severity factors are patient-related (poor or fragile vascular conditions), and technique-related (use of a power injector, large volume). It is important to identify these factors, optimise the injection site and technique accordingly, and monitor the injection prior to, during and after the injection of XENETIX.

4.4.1.2. Precautions for use

4.4.1.2.1. Intolerance to iodinated contrast agents:

Prior to the examination:

- identify at-risk subjects by asking specific questions about their history.

Corticosteroids and H1 antihistamines have been suggested as premedication in patients with the highest risk of intolerance reactions (those with known intolerance to an iodinated contrast agent). However, they do not prevent severe or fatal anaphylactic shock. During the examination, the following measures must be in place:

- medical surveillance
- in situ venous access

After the examination:

- After contrast agent administration, the patient must be observed for at least 30 minutes, as the majority of serious adverse reactions occur within this time frame.
- The patient must be informed of the potential for delayed reactions (up to 7 days) (see Section 4.8 Undesirable effects).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), Lyell's syndrome (toxic epidermal necrolysis or TEN) and acute generalised exanthematous postulosis (AGEP), potentially life-threatening, have been reported in patients to whom Xenetix had been administered (see section 4.8, Undesirable effects). When initiating the treatment, patients should be informed of the signs and symptoms and should be monitored closely to detect serious adverse skin reactions. Xenetix should be discontinued immediately if a severe hypersensitivity reaction is suspected. In the event of a severe cutaneous adverse reaction in a patient taking Xenetix, Xenetix should never be re-administered to this patient (see Section 4.3).

4.4.1.2.2. Renal impairment

Iodinated contrast agents may cause temporary changes in renal function or worsen pre-existing renal impairment. Preventive measures are as follows:

- Identify at-risk patients, i.e., with dehydration, renal insufficiency, diabetes, severe heart failure, monoclonal gammopathy (multiple myeloma, Waldenstrom's macroglobulinemia), history of renal failure after contrast agent administration; infants below the age of one year and elderly subjects with atheroma.
- Hydrate as necessary using an appropriate quantity of saline solution.
- Avoid combinations with nephrotoxic medicinal products. If this combination is necessary, increase biological renal monitoring. The medicines products concerned include aminosides, organoplatinum compounds, high dose methotrexate, pentamidine, foscarnet and certain antivirals (aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir), vancomycin, amphotericin B, immunosuppressants such as ciclosporin, tacrolimus and ifosfamide.

- Allow at least 48 hours between radiological examinations with contrast agent injections or delay further examinations until renal function returns to baseline.
- Prevent lactic acidosis in diabetics treated with metformin, by monitoring serum creatinine levels. Normal renal function: metformin is discontinued when the contrast agent is administered, for a period of at least 48 hours or until normal renal function is restored. Abnormal renal function: metformin is contraindicated. In an emergency: if the examination cannot be avoided, precautions must be taken: discontinuation of metformin, hydration, renal function monitoring and monitoring for signs of lactic acidosis.

Haemodialysis patients can receive iodinated contrast agents, as these products are dialysable. Consult with the haemodialysis department prior to administration.

4.4.1.2.3. Hepatic insufficiency

Particular attention is required when a patient presents with both hepatic and renal insufficiency since, in this situation, the risk for retention of contrast agent is increased.

Care should be taken in renal or hepatic impairment, diabetes or in patients with sickle cell disease.

Adequate hydration should be ensured in all patients before and after contrast media administration and particularly in patients with renal impairment or diabetes where it is important to maintain hydration to minimise deterioration in renal function.

4.4.1.2.4. Asthma

It is recommended that asthma be brought under control before the injection of an iodinated contrast agent.

Due to an increased risk of bronchospasm, special caution should be taken in patients who suffered an asthmatic attack within 8 days prior to the examination.

4.4.1.2.5. Disturbed thyroid function

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism. See also section on Paediatric population.

Paediatric population:

Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age

Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media (ICM) in pediatric patients 0 to 3 years of age.

Younger age, very low birth weight, prematurity, underlying medical conditions affecting thyroid function, admission to neonatal or pediatric intensive care units, and congenital cardiac conditions are associated with an increased risk of hypothyroidism after ICM exposure. Pediatric patients with congenital cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures.

An underactive thyroid during early life may be harmful for cognitive and neurological development and may require thyroid hormone replacement therapy. After exposure to ICM, individualize thyroid function monitoring based on underlying risk factors, especially in term and preterm neonates.

4.4.1.2.6. Cardiovascular diseases (see Section 4.8 Undesirable effects)

In patients with cardiovascular disease (such as early or patent heart failure, coronaropathy, pulmonary hypertension, valvular heart disease, cardiac arrhythmias), the risk of cardiovascular reactions is increased after administration of an iodinated contrast agent. Intravasal injection of the contrast medium may cause pulmonary oedema in patients with manifest or incipient heart failure, whereas administration in pulmonary hypertension and heart valve disorders may result in marked changes in haemodynamics. The frequency and degree of severity appear to be related to the severity of the cardiac disorders. In case of severe and chronic hypertension, the risk of renal damage secondary to the administration of the contrast medium and also due to the catheterization itself may be increased. Careful evaluation of the risk-benefit ratio is necessary in these patients.

4.4.1.2.7. Central nervous system disorders

The benefit-to-risk ratio must be evaluated in each case:

- due to the risk of aggravation of neurological symptoms in patients with transient ischaemic attack, acute cerebral infarction, recent intracranial haemorrhage, cerebral oedema, or idiopathic or secondary (tumour, scar) epilepsy.
- if the case of intra-arterial use in alcoholics (acute or chronic alcoholism) and in people addicted to other substances.

4.4.1.2.8. Pheochromocytoma

Patients with pheochromocytoma may develop a hypertensive crisis after intravascular administration of a contrast agent and require appropriate management prior to the examination.

4.4.1.2.9. Myasthenia gravis

Administration of a contrast agent may worsen the symptoms of myasthenia gravis.

4.4.1.2.10. Increased adverse reactions

Undesirable effects linked to iodinated contrast agent administration may be intensified in patients showing pronounced agitation, anxiety and pain. Appropriate management may be necessary, up to and including sedation.

4.4.1.2.11. Excipients

This medicine contains sodium. It contains less than 1 mmol sodium per 100 mL i.e., it is essentially “sodium-free”.

4.5. Interaction with other medicinal products and other forms of interaction

4.5.1. Medicinal products

+ **Metformin in diabetics** (see Section 4.4 Precautions for use — renal insufficiency).

+ **Radiopharmaceuticals** (see Section 4.4 Warnings)

Iodinated contrast agents disrupt radioactive iodine uptake by thyroid tissue for several weeks, which may lead to impaired uptake in thyroid scintigraphy and decreased efficacy of iodine 131 treatment.

In patients due to undergo renal scintigraphy with injection of a radiopharmaceutical secreted by the renal tubules, it is preferable to carry out the scintigraphy before iodinated contrast agent injection.

+ **Beta blockers**, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists.

These medicinal products lead to a decrease in the efficacy of the cardiovascular compensatory mechanisms for blood pressure disorders: the doctor must be informed before the injection of iodinated contrast agent and have resuscitation equipment to hand.

+ **Diuretics**

Due to the risk of diuretic-induced dehydration, prior rehydration with fluids and electrolytes is necessary to limit the risk of acute renal failure.

+ **Interleukin 2**

There is a risk of increased reaction to contrast agents following recent treatment with interleukin 2 (intravenous route): rash or, more rarely, hypotension, oliguria, or even renal failure.

4.5.2. Other forms of interaction

High concentrations of iodinated contrast agent in plasma and urine may interfere with *in vitro* measurements of bilirubin, proteins and inorganic substances (iron, copper, calcium and phosphate); it is recommended that these assays are not be performed within 24 hours of the examination.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no or few data (less than 300 pregnancy outcomes) on the use of iodridol in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of XENETIX during pregnancy.

Temporary iodine overload following administration of the product to the mother may lead to foetal dysthyroidism if the examination takes place after 14 weeks of pregnancy. However, in view of the reversibility of the effect and the expected benefit to the mother,

the isolated administration of an iodinated contrast agent is justifiable if the indication for the radiological examination in a pregnant woman has been carefully evaluated.

In neonates who have been exposed to iodinated contrast media in utero, it is recommended to monitor thyroid function (see section 4.4).

Lactation

Iodinated contrast agents are excreted in breast milk in very small amounts. Consequently, isolated administration to the mother involves a minor risk of adverse reactions in the infant. It is preferable to suspend breastfeeding for 24 hours after administration of the iodinated contrast agent.

Fertility

A study conducted on rats does not indicate any effects on reproductive function.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

During clinical studies on 905 patients, 11% of patients experienced an adverse reaction related to administration of XENETIX (apart from feeling of warmth), the most common being pain, injection site pain, bad taste in the mouth and nausea.

Adverse reactions related to the use of XENETIX are generally mild to moderate, and transient.

The adverse reactions most commonly reported during administration of XENETIX since marketing are a feeling of warmth, and pain and oedema at the injection site.

Hypersensitivity reactions are usually immediate (during the injection or over the hour following the start of the injection) or sometimes delayed (one hour to several days after the injection), and then appear in the form of adverse skin reactions.

Immediate reactions comprise one or several, successive or concomitant effects, usually including skin reactions, respiratory and/or cardiovascular disorders, which may be the first signs of shock, and can be fatal in rare cases.

Severe heart rhythm disorders including ventricular fibrillation have been very rarely reported in heart disease patients, and outside the context of hypersensitivity (see Section 4.4 Precaution for use).

The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). The frequencies presented are from the data of an observational study on 352,255 patients.

System Organ Class	Frequency: adverse reaction
Immune system disorders	Rare: hypersensitivity Very rare: anaphylactic shock, anaphylactoid reaction, anaphylactic reaction
Endocrine disorders	Very rare: thyroid disorders Not known: transient neonatal hypothyroidism, hypothyroidism***
Nervous system disorders	Rare: presyncope (vasovagal reaction), tremor*, paresthesia* Very rare: coma*, convulsions*, confusion*, visual disorders*, amnesia*, photophobia*, transient blindness*, drowsiness*, agitation*, headache Not known: dizziness**
Ear and labyrinth disorders	Rare: dizziness Very rare: hearing impaired
Cardiac disorders	Rare: tachycardia, bradycardia Very rare: cardiac arrest, myocardial infarction (more frequent after intracoronary injection), arrhythmia, ventricular fibrillation, angina pectoris, Torsades de Pointes, coronary arteriospasm
Vascular disorders	Rare: arterial hypotension (low blood pressure), high blood pressure Very rare: circulatory collapse Not known: cyanosis**
Respiratory, thoracic and mediastinal disorders	Rare: dyspnoea, cough, tightness in the throat, sneezing Very rare: respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, laryngeal oedema
Gastrointestinal disorders	Uncommon: nausea Rare: vomiting Very rare: abdominal pain
Skin and subcutaneous tissue disorders	Rare: angioedema, urticaria (localised or extensive), erythema, pruritus Very rare: Acute Generalized Exanthematous Pustulosis, Stevens-Johnson syndrome, Lyell's syndrome, eczema, maculopapulous exanthema (all as delayed hypersensitivity reactions) (see Section 4.4) Undetermined frequency: systemic drug hypersensitivity syndrome with eosinophilia (DRESS) and systemic symptoms (see Section 4.4).
Renal and urinary disorders	Very rare: acute renal insufficiency, anuria
General disorders and administration site conditions	Uncommon: feeling of warmth Rare: facial oedema, malaise, chills, injection site pain

	Very rare: injection site necrosis following extravasation, injection site inflammation following extravasation, injection site oedema
Investigations	Very rare: blood creatinine increased

*Examinations during which the iodinated contrast agent concentration in cerebral arterial blood is high.

**Effect most often reported in the context of a hypersensitivity reaction.

***Transient hypothyroidism has been reported in younger children after exposure to iodine-based contrast agents (see Section 4.4)

As described in Section 4.4, compartment syndrome may be observed after extravasation.

The following adverse reactions were reported for other water-soluble iodinated contrast agents:

System Organ Class	Frequency: adverse reaction
Nervous system disorders	Paralysis, paresis, speech disorders
Psychiatric disorders	Hallucinations
Gastrointestinal disorders	Acute pancreatitis (after ERP), abdominal pain, diarrhoea, parotid gland enlargement, salivary hypersecretion, dysgeusia
Skin and subcutaneous tissue disorders	Erythema multiforme
Vascular disorders	Thrombophlebitis
Investigations	abnormal electroencephalogram, blood amylase increased

Cardiovascular collapse of variable severity may occur immediately with no warning signs or may complicate the cardiovascular symptoms mentioned in the above table.

Abdominal pain and diarrhoea, not reported for XENETIX, are linked mainly to administration via the oral or rectal route.

Local pain and oedema may occur at the injection site without extravasation of the injected product and are benign and transient.

During intra-arterial administration, the sensation of pain at the injection site depends on the osmolality of the product injected.

Paediatric population

The expected nature of the undesirable effects related to Xenetix is the same as that of the effects reported in adults. Their frequency cannot be estimated from the available data.

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/> and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9. Overdose

In the event of very high doses, fluid and electrolyte loss must be compensated by appropriate rehydration. Renal function must be monitored for at least three days. Haemodialysis may be carried out if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: IODINATED CONTRAST AGENT

ATC code: V08AB11

XENETIX 250 is a urographic and angiographic water-soluble nonionic contrast agent with an osmolality of 585 mOsm/kg.

XENETIX 300 is a urographic and angiographic water-soluble nonionic contrast agent with an osmolality of 695 mOsm/kg.

XENETIX 350 is a urographic and angiographic water-soluble nonionic contrast agent with an osmolality of 915 mOsm/kg.

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

Injected via the intravascular route, iobitridol is distributed through the vascular system and interstitial space. In humans, the elimination half-life is 1.8 h, the distribution volume is 200 mL/kg and the total clearance is 93 mL/min on average. Binding to plasma proteins is low (< 2%). It is mainly eliminated by the kidneys (glomerular filtration without reabsorption or secretion at tubule level) in unchanged form.

The osmotic diuresis induced by XENETIX is related to the osmolality and the volume injected.

In the event of renal insufficiency, elimination is mainly by biliary route. The substance is dialysable.

5.3. Preclinical safety data

Toxicology studies using the intravenous route did not reveal any adverse effects except under conditions that differ considerably from those used clinically (dose repetitions). In the case of iobitridol as with all tri-iodinated, non-ionic and water-soluble contrast agents administered in single large-volume doses (25- 50 mL/kg) these effects manifest as transient signs of hypothermia, respiratory depression or dose-dependent histological signs in the target organs (liver, kidneys), such as hepatocellular vacuolisation, and tubular ectasia.

Repeated dose administration in dogs for 28 days at high doses (8 ml/kg) resulted in granular and vacuolar degeneration, which was reversible after discontinuation of treatment.

Local irritation may be observed in the event of perivascular infiltration.

The substance was not found to be mutagenic under the test conditions used. Animal studies have shown no toxic effects on fertility, reproductive performance and embryofetal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Trometamol hydrochloride, trometamol, Sodium calcium edetate, , hydrochloric acid or sodium hydroxide, water for injection.

6.2. Incompatibilities

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

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 below 30°C.

6.5. Nature and content of container

XENETIX 250

50 mL, 100 mL, 200 mL or 500 mL glass bottles with chlorobutyl rubber stoppers.

XENETIX 300, XENETIX 350

20 mL, 50 mL, 60 mL, 100 mL, 150 mL, 200 mL or 500 mL glass bottles with chlorobutyl rubber stoppers.

Not all pack sizes may be marketed.

6.6. Instructions for disposal and handling

No special requirements for disposal.

7. MANUFACTURER

Lab. Guerbet, France.

BP 57400, F-95943 ROISSY CdG, CEDEX, 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.

Hashiloach 6, POB 3340, Petach-Tikva.

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Xenetix SPC vr 02A