Package leaflet
Xenetix®, solution for injection

1. NAME OF THE MEDICINAL PRODUCT

XENETIX®, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Xenetix® 250 (250mg iodine/ ml)	Per 100ml of solution: Iobitridol ……. 54.84g (548.4mg/ml) Corresponding mass of iodine … 25g (250mg/ml) Viscosity at 20°C: 6 mPa.s Viscosity at 37°C: 4 mPa.s Osmolality: 585 mOsm/kg H_2O
Xenetix® 300 (300mg iodine/ ml)	Per 100ml of solution: Iobitridol ……. 65.81g (658.1mg/ml) Corresponding mass of iodine … 30g (300mg/ml) Viscosity at 20°C: 11mPa.s Viscosity at 37°C: 6mPa.s Osmolality: 695mOsm/kg H_2O
Xenetix® 350 (350mg iodine/ ml)	Per 100ml of solution: Iobitridol ……..… 76.78g (767.8mg/ml) Corresponding mass of iodine … 35g (350mg/ml) Viscosity at 20°C: 21mPa.s Viscosity at 37°C: 10mPa.s Osmolality: 915mOsm/kg H_2O

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.
Contrast agent for use in:

Xenetix® 250	Xenetix® 300	Xenetix® 350
- Intravenous digital subtraction angiography	- Intravenous urography - Intravenous digital	- Intravenous urography - Intravenous digital

	subtraction angiography - Arthrography - Hysterosalpingography	subtraction angiography

4.2. Posology and method of administration

The doses must be adapted to the examination and the regions to be opacified, as well as to the body weight and renal function of the subject.
There is no data about the use of Xenetix in pediatric patients. Therefore, the use of Xenetix is not recommended in pediatric patients.
Usually the same iodine concentration and volume are used as with other iodinated X-ray contrast in current use. As with all contrast media, the lowest dose necessary to obtain adequate visualisation should be used.
Adequate hydration should be assured before and after administration as for other contrast media.
Usually, the rate of administration varies between 0.5 and 5 ml/s depending on the type of examination.

Xenetix® 250
Recommended mean dosages for intravascular routes:

Indications	Mean dose (ml/kg)	Total volume range (ml)
Intravenous digital subtraction angiography	3.1	75-360

Xenetix® 300
Recommended mean dosages for intravascular routes:

Indications	Mean dose (ml/kg)	Total volume range (ml)
Urography with: - rapid i.v. injection - slow i.v. injection	 1.2 1.6	 50-100 100
Intravenous digital subtraction angiography	1.7	40-270

Xenetix® 300
Recommended mean dosages for intracavitary routes:

Indications	Mean volume (ml)	Comments
Arthrography	5 to 20	Intraarticular route Volume adapted to the joint
Hysterosalpingography	5 to 20	Intrauterine route Dose to be adapted to the uterine volume

Xenetix® 350

Recommended mean dosages for intravascular routes:

Indications	Mean dose (ml/kg)	Total volume range (ml)
Intravenous urography	1.0	50-100
Intravenous digital subtraction angiography	2.1	95-250

4.3. Contraindication

- Hypersensitivity to iobitridol or any of the excipients.
- History of a major immediate reaction or delayed skin reaction to a Xenetix® injection.
- Manifest thyrotoxicosis
- In the absence of specific studies, myelography is not an indication for Xenetix®.
- Hysterosalpingography during pregnancy is contraindicated for Xenetix® 300.

4.4. Special warnings and special precautions of use

- There is a risk of allergic reactions regardless of the route of administration or the dose.
- The risk of allergic reactions associated with products administered locally for opacification of body cavities is not clear-cut:

a) Administration via certain specific routes (articular, intra-uterine, etc.) results in varying degrees of systemic diffusion, i.e. systemic effects may be observed.

b) However, the allergic immune mechanism is not dose-dependent and immuno-allergic reactions may occur at any time, regardless of the administration route.

4.4.1. General particulars corresponding 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 can cause minor or major reactions that can be life-threatening. They may occur immediately (within 60 minutes) or be delayed (up to 7 days). They are often unpredictable.

Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use.

Several mechanisms have been evoked to explain the occurrence of these reactions:

- direct toxicity affecting the vascular endothelium and tissue proteins.
- pharmacological action modifying the concentration of certain endogenous factors (histamine, complement factors, inflammation mediators), observed more frequently with hyperosmolar contrast media.
- immediate IgE-mediated allergic reactions to the contrast agent Xenetix (anaphylaxis)
- allergic reactions due to a cellular-type mechanism (delayed cutaneous reactions)

Patients who have already experienced a reaction during administration of an iodinated contrast agent are at higher risk of experiencing another reaction following administration of the same or possibly a different iodinated contrast agent, and are thus considered to be at-risk patients.

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

Before administering an iodinated contrast agent, it is important to ensure that the patient is not scheduled to undergo a scintigraphic examination or laboratory tests related to the thyroid or to receive radioactive iodine for therapeutic purposes.

Administration of contrast agents via any route disrupts thyroid hormone concentrations and iodine uptake by the thyroid or by metastases of thyroid cancer, until urine iodine levels have returned to normal.

Other warnings

Extravasation is an uncommon complication (0.04% to 0.9%) of intravenous injections of contrast media. More frequent 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, optimize 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 patients by a precise screening of histories.

Corticosteroids and H1-type antihistamines have been suggested as premedication in patients presenting with the highest risk for intolerance reactions (history of intolerance to an iodinated contrast agent). However, they do not prevent the occurrence of serious or fatal anaphylactic shock. During the procedure, the following measures must be maintained:

- medical surveillance
- permanent venous access.

After the examination:

- After administration of the contrast agent, the patient must be monitored for at least 30 minutes, since most serious adverse reactions occur within this time period.
- The patient must be informed of the possibility of delayed reactions (for up to seven days) (see Section 4.8 Undesirable effects)

4.4.1.2.2. Renal insufficiency

Iodinated contrast agents can induce a transient alteration in renal function or worsen pre-existing renal insufficiency. Preventive measures include:

- Identify at-risk patients, i.e. with dehydration or renal insufficiency, diabetes, severe heart failure, monoclonal gammapathy (multiple myeloma, Waldenstrom's macroglobulinemia), a history of renal failure after iodinated contrast agent administration, children under one year of age and elderly subjects with atheroma.
- Hydrate when necessary using a saline solution.
- Avoid combinations with nephrotoxic medicines. If this cannot be avoided, laboratory monitoring of renal function must be intensified. The medicines concerned include aminoglycosides, organoplatinum compounds, high doses of methotrexate, pentamidine, foscarnet and certain antiviral agents [aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir], vancomycin, amphotericin B, immunosuppressants such as cyclosporine or tacrolimus, ifosfamide)

- Allow at least 48 hours between two radiological examinations with injection of contrast agents, or postpone any new examination until renal function returns to baseline.
- Prevent lactic acidosis in diabetics treated with metformin, by monitoring serum creatinine levels. Normal renal function: treatment with metformin must be suspended before contrast agent injection and for at least 48 hours after or until normal renal function is restored. Abnormal renal function: metformin is contraindicated. In case of emergency: if the examination is mandatory, precautions must be taken, i.e. metformin discontinuation, hydration, monitoring of renal function and checking for signs of lactic acidosis.

Iodinated contrast agents can be used in haemodialysed patients as the agents are removed by dialysis. Prior approval should be obtained from the haemodialysis department.
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.

4.4.1.2.3. Hepatic insufficiency

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

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

4.4.1.2.4. Asthma

Stabilisation of asthma is recommended 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 eight days prior to the examination,.

4.4.1.2.5. Dysthyroidism

After iodinated contrast agent injection, particularly in patients with a goitre or a history of dysthyroidism, there is a risk either of a flare-up of hyperthyroidism or development of hypothyroidism. There is also a risk of hypothyroidism in neonates who have received, or whose mother has received, an iodinated contrast agent.

4.4.1.2.6. Cardiovascular disorders (see Section 4.8 Undesirable effects)

In patients with cardiovascular disease (such as early or patent heart failure, coronaropathy, pulmonary hypertension, valvulopathy, cardiac arrhythmias), the risk of cardiovascular reactions is increased after administration of an iodinated contrast agent. Intravascular 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 related to the severity of the cardiac disorders. In case of severe and chronic hypertension, the risk of renal damage due to administration of the contrast medium and also due to the catheterisation itself may be increased. Careful weighing up 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 for each case:

- due to the risk of aggravation of neurological symptoms in patients with a transient ischaemic attack, acute cerebral infarct, recent intracranial haemorrhage, cerebral oedema, or idiopathic or secondary (tumour, scar) epilepsy.
- if the intra-arterial route is used in an alcoholic patient (acute or chronic alcoholism) and other drug-addicted subject.

4.4.1.2.8. Phaeochromocytoma

Patients with phaeochromocytoma may develop a hypertensive crisis after intravascular administration of a contrast agent, and must be monitored prior to the examination.

4.4.1.2.9. Myasthenia

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

4.4.1.2.10. Intensification of side effects

Adverse reactions related to iodinated contrast agent administration may be intensified in patients showing pronounced agitation, anxiety and pain. Appropriate management such as sedation may be necessary.

4.4.1.2.11. Excipients

This medicinal product contains sodium. It contains less than 1 mmol sodium per 100 mL, i.e. essentially "sodium-free".

4.4.2. Warnings and precautions for use specific to certain administration routes with appreciable systemic diffusion

4.4.2.1. Products administered via the intra-uterine route (For Xenetix® 300)

Contraindication

Pregnancy for hysterosalpingography.

Special precautions for use

In the interview and with appropriate tests, systematically check for possible pregnancy in women of childbearing age. Exposure of the female genital routes to x-rays must be subject to careful evaluation of the benefit-to-risk ratio.

In the event of inflammation or acute pelvic infection, hysterosalpingography can only be performed after a careful assessment of the benefit-to-risk ratio.

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

4.5.1. Medicinal products

+ Metformin in diabetics (see Section 4.4.1.2.2. Precautions for use - renal insufficiency).

+ Radiopharmaceuticals (see Section 4.4.1.1. Warnings)

Iodinated contrast agents alter the uptake of radioactive iodine by the thyroid for several weeks, which may on the one hand result in diminished uptake in thyroid scintigraphy and on the other hand decrease the efficacy of iodine 131 treatment. In patients scheduled to undergo renal scintigraphy with injection of

a radiopharmaceutical excreted by the renal tubules, it is preferable to carry out this examination before injecting the iodinated contrast agent.

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

These medicinal products reduce the efficacy of the cardiovascular compensation mechanisms that occur in haemodynamic disorders. The physician must be aware of this before injecting the iodinated contrast agent and appropriate intensive care equipment must be available.

+ Diuretics

Due to the risk of dehydration provoked by diuretics, rehydration with water and electrolytes must be carried out prior to the examination in order to limit the risk of acute renal failure.

+ Interleukin 2

The risk of developing a reaction to the contrast agents is increased if the patient has recently been treated with interleukin 2 (intravenous route), i.e. rash or, more rarely, hypotension, oliguria, or even renal failure.

4.5.2. Other forms of interaction

High concentrations of iodinated contrast agents in plasma and urine may interfere with the *in vitro* determination of bilirubin, proteins and inorganic substances (iron, copper, calcium and phosphate). It is recommended that these determinations should not be carried out within 24 hours following the examination.

4.6. Pregnancy and Lactation

In the interview and with appropriate tests, systemically check for possible pregnancy in women of childbearing age. Exposure of the female genital routes to x-rays must be subjected to careful evaluation of the benefit-to-risk ratio.

Hysterosalpingography with Xenetix® 300 during pregnancy is contraindicated.

Embryotoxicity

Animal studies have not shown any teratogenic effects.

In the absence of any teratogenic effects in animal species, no malformative effect is expected in humans. To date, substances causing malformations in humans have always proved to be teratogenic in animals during studies properly conducted in two species.

Foetotoxicity

The transient iodine overload following administration to the mother may induce foetal dysthyroidism if the examination takes place after more than 14 weeks of amenorrhoea. However, in view of the reversibility of the effect and 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.

Mutagenicity and fertility

The product was not found to be mutagenic under the test conditions used.

No data on reproductive function are available.

Lactation

Iodinated contrast agents are only excreted in breast milk in very small amounts. Isolated administration to the mother consequently involves a minor risk of adverse reactions in the infant. It is advisable to stop breastfeeding for 24 hours after administration of the iodinated contrast agent.

4.7. Effects on ability to drive and use machine

No particular risks are known.

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 and nausea.

Undesirable effects 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 feeling of warmth, and pain and oedema at the injection site.

The 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, which can rarely be fatal.

Severe rhythm disorders including ventricular fibrillation have been very rarely reported in heart disease patients, in as well as out of a context of hypersensitivity (see Section 4.4. Special warnings and special precautions of use)

The adverse reactions are listed in the table below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥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 derived from the data of an observational study on 352,255 patients.

System Organ Class	**Frequency: adverse reaction**
Immune system disorders	Rare: hypersensitivity Very rare: anaphylactoid reaction, anaphylactic reaction
Endocrine disorders	Very rare: thyroid disorder
Nervous system disorders	Rare: presyncope (vasovagal reaction), tremor*, paresthesia* Very rare: coma*, convulsions*, confusion*, visual disorders*, amnesia*, photophobia*, transient blindness*, somnolence*, agitation*, headache
Ear and labyrinth disorders	Rare: vertigo Very rare: hearing impaired
Cardiac disorders	Rare: tachycardia Very rare: cardiac arrest, myocardial infarction (more frequent

	after intracoronary injection), arrhythmia, ventricular fibrillation, angina pectoris
Vascular disorders	Rare: hypotension Very rare: circulatory collapse
Respiratory, thoracic and mediastinal disorders	Rare: dyspnoea, cough, tightness in the throat, sneezing Very rare: respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, laryngeal oedema Unknown: rhinitis
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 Generalised Exanthematous Pustulosis, Stevens-Johnson syndrome, Lyell's syndrome, eczema, maculopapulous exanthema (all as delayed hypersensitivity reactions)
Renal and urinary disorders	Very rare: acute renal failure, anuria
General disorders and administration site conditions	Uncommon: feeling hot Rare: facial oedema, malaise, chills, injection site pain Very rare: injection site necrosis following extravasation, injection site oedema, injection site inflammation following extravasation
Investigations	Very rare: blood creatinine increased

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

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

System Organ Class	**Frequency: adverse reaction**
Nervous system disorders	Paralysis, paresis, hallucinations, speech disorders
Gastrointestinal disorders	Abdominal pain, diarrhoea, parotid gland enlargement, salivary hypersecretion, dysgeusia
Skin and subcutaneous tissue disorders	Erythema multiforme
Vascular disorders	Thrombophlebitis
Investigations	Electroencephalogram abnormal, blood amylase increased

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

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.

Undesirable effects related to specific examinations: (For Xenetix® 300)

Arthrography: arthralgias were frequently reported during clinical studies (4%).
Hysterosalpingography: pelvic pain was frequently reported during clinical studies (3%).

4.9. Overdose

If a very high dose of contrast agent is administered, the water and electrolyte loss must be compensated by suitable rehydration. Renal function must be monitored for at least three days. Haemodialysis may be performed if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

IODINATED CONTRAST AGENT
(V: other) ATC code: V08AB11
Xenetix® is a urographic and angiographic water-soluble nonionic contrast agent.

5.2. Pharmacokinetic properties

After intravascular injection, iobitridol is distributed in the intravascular system and interstitial compartment. In humans, the elimination half-life is 1.8 h, the volume of distribution is 200 ml/kg and the total clearance is 93 ml/min (mean values). Binding to plasma proteins is negligible (< 2%). It is mainly eliminated via the kidneys (glomerular filtration without tubular reabsorption or secretion) in unchanged form. The osmotic diuresis induced by Xenetix® is dependent on the osmolality and the volume injected.
In patients with renal insufficiency, elimination occurs mainly via the biliary route. The substance can be dialysed.

5.3. Preclinical safety data

Toxicological results for intravenous use show an absence of effects, or effects occurring under conditions much more extreme than those recommended for clinical use (dosage, repeated doses). Following the single administration of high doses (9 to 18 gI/kg), Xenetix caused transient signs of hypothermia, respiratory depression and dose-dependent histological lesions that occurred in the target organs (liver, kidney) and included hepatocellular vacuolisation, and tubular vacuolisation and dilation. Following repeated administration of high doses (2.8 gI/kg) for 28 days in dogs, granular vacuolar degeneration that was reversible after discontinuation of treatment was observed.
Local irritation could be observed in the event of extravasation.
Animal studies did not demonstrate any teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium calcium edetate, trometamol, trometamol hydrochloride, sodium hydroxide or hydrochloric acid, 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

Three years.

6.4. Special precaution for storage

- Keep out of the reach and sight of children.
- Vials/bottles: Do not store above 30°C and protect from light.
- Do not use after the expiry date given on the vial.

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