XENETIX®

lobitridol

Product monograph

Flow of **contrast**

Guerbet

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XENETIX®

Iobitridol

Contrast agent for radiographic imaging

Product **Monograph**

Contents

XENETIX® summarised

As a non-ionic low-osmolar contrast agent, **XENETIX®** offers a significant safety advantage over older ionic, high-osmolar iodinated contrast agents. In fact, the molecular structure of **XENETIX®** is optimized to provide good safety without compromising efficacy.

It has been proposed that the stabilized hydrophilicity of the **XENETIX®** molecule may result in a low risk of interaction with biological membranes, and this could in theory reduce the risk of chemotoxicity frequently associated with other iodinated contrast agents.

The iodine atoms contained in each **XENETIX®** molecule provides its radiopacity, and therefore its image-enhancing efficacy.

XENETIX® represents the optimal combination of 4 characteristics that are inter related and cannot be independently optimized: high hydrophilicity, optimized iodine concentration, low osmolality and moderate viscosity. This combination impacts on the diagnostic efficacy and total amount of iodine needed, on the hydrophilicity and interaction with the body systems and on tolerability.

In the clinical setting, this physicochemical property translates into good image quality and diagnostic efficacy as demonstrated in numerous comparative clinical trials in adult patients versus other non-ionic low osmolar contrast agents such as iohexol and iomeprol. The good renal safety of **XENETIX®** has also been demonstrated in patients with renal failure and in paediatric populations versus iso-osmolar contrast agents such as iodixanol.

Finally, four retrospective pooled, post-marketing studies, including more than 320,000 patients aged between a few weeks and 101 years, concluded that **XENETIX®** is well tolerated and safe to use.

XENETIX® is available in a range of concentration, either in a glass vial or in the easy-to-use and eco-friendly **ScanBag®** and in a range of packaging sizes so that the volume can be easily adapted to the individual patient. **XENETIX®** is approved for use in many types of computed tomography (CT) and other radiological examinations for diagnoses and investigations in numerous therapeutic areas including urology, oncology, cardiology and neurology.

XENETIX® 300 and **XENETIX®** 350 are indicated for use in head and whole body CT and digital subtraction angiography (DSA) via the intravenous (IV) route, and in arteriography or cardiac angiography via the intra-arterial (IA) route; in addition, **XENETIX®** 350 can be used in IV urography.

XENETIX® has also been used in more sophisticated imaging techniques, such as multi-detector CT (MDCT) or multi-slice CT (MSCT), and has been found to offer the advantage of equivalent efficacy at a lower total iodine dose than more concentrated contrast agents.

1. Introduction on medical imaging and iodinated contrast agents

Medical imaging is used in the diagnosis and during the treatment of diseases. It enables clear differentiation of anatomical structures and detection of abnormalities [1]. Imaging techniques have become less invasive and more sophisticated, resulting in more timely and accurate diagnosis [2]. Depending on their distribution profile, water-soluble iodinated contrast agents are widely used to improve the contrast between the different tissues [3]. Intravascular contrast agents are used in millions of radiological examinations each year [4].
A brief overview on radiographic imaging and iodinated contrast agents is provided thereafter.

1.1 Medical radiographic imaging

X-rays are used to visualize an anatomical structure or function of the human body in medical radiographic imaging [5].

The invention of the scanner by A.M. Cormack and G.M. Hounsfield is as important as the discovery of x-rays by Roentgen in 1895. X-ray scanography can be defined as the method used to obtain a density measurement of the elementary volumes of a cross section of anatomical structure. This method enables a more precise measurement of the density than conventional x-ray radiography. Since 1998, Multi-Detector row Computerized Tomography (MDCT) has dramatically improved imaging through both anatomical and functional assessments of the body as well as diagnosis of cardiovascular disease and tumors.
This technique allows acquisition of a volume of body or organ, rather than slices [6].The latest MDCT scanners produce an image with high spatial resolution, within a submillimeter-isotropic volume of a large body area in a few seconds. The raw data can be reconstructed into an image in any anatomical plane [7]. However, CT is based on x-rays and therefore still has a number of drawbacks compared with Magnetic Resonance Imaging (MRI). Even though MRI represents an alternative (avoiding ionising radiation) or complements it for specific indications (imaging soft tissue), MRI cannot replace CT in all indications [7]. In order to fully exploit the advantages of the new generation of MDCT scanners, the acquisition, contrast agent-related and patient-related parameters have to be individually optimized.

Water-soluble intravascular contrast agents injected in the vascular compartment enhance the imaging of blood vessels and parenchymal organs, and allow for visualization and differentiation of anatomical structures [1]. These contrast agents block or slow down the passage of x-rays and consequently increase the opacification of the relevant portions of the image, resulting in a positive contrast image [5]. Those in use today are based on iodine, an atom with high x-ray attenuation, and are discussed in section 1.2. Many patient-related factors can affect contrast enhancement and include, for example, body mass, blood volume and cardiac output. Contrast agent-related parameters that affect contrast enhancement are contrast volume (mL), contrast agent concentration (mg I /mL), injection rate

(mL/s) and scan delay (s). Rapid advances in scanning technology have led to the development of more sophisticated contrast agent injection protocols[1].

Contrast-enhanced CT is an indispensable part of CT examinations in oncology. Imaging is useful in oncology to detect cancer, stage or grade tumours and monitor effects of treatment. Oncological applications include, for example, CT angiography for visualization of the arterial supply to the liver, vascular encasement in lung or pancreatic cancer for tumour staging, and CT perfusion imaging where sequential scans are performed during contrast injection to estimate perfusion of the tumour (e.g. in brain tumours)[1].
CT is the standard method for detection of renal cell carcinoma and acute ureterolithiasis and MDCT can produce 3-D images of the entire urinary tract[2]. A recent survey reported that CT urography is becoming more popular, and in some radiology centres has largely replaced IV urography for urinary tract imaging[8]. A 3-phase technique that consists of an unenhanced CT scan (first phase), followed by a single contrast agent bolus at 3 mL/s with two subsequent CT scans (nephrographic and excretory phases) was the most common CT urography technique in this survey[8].

CT is used in cardiac examinations, with advances in MDCT technology from 16-detector to 320 detector scanners, yielding improved accuracy and diagnostic capability in CAD (Coronary Artery Disease) diagnosis. Calcium scoring using cardiac CT is used as a prognostic test for determining the risk of coronary events. Cardiac CT is also used, particularly in emergency departments, to rule out aortic dissection, pulmonary embolism, and acute coronary syndrome[9].

1.2 Iodinated contrast agents

Water-soluble iodinated contrast agents are sterile iodine-containing solutions[10] and are the most frequently used intravascularly[11]. Their iodine content is responsible for their radiopaque properties[12]. Iodinated contrast agents offer the good compromise between efficacy and safety.

First generation «conventional» iodinated contrast agents have been available for about 50 years[12], and are sodium and meglumine salts of tri-iodinated benzoic acid[13]. They have a monomeric structure and are mainly ionic (dissociate in water), therefore hyperosmolar in solution. They are known as hyperosmolar contrast agents (HOCM) because their osmolality is 6–7 times that of human plasma[14] depending on their iodine concentration. Table 1 shows their physical and chemical properties. HOCM are associated with haemodynamic and chemotoxic effects because of their hyperosmolar nature[13], resulting in potential adverse events such as acute kidney injury, pulmonary oedema, cardiovascular collapse, and cardiac arrhythmia[15]. Table 2 overviews adverse events occuring with iodinated contrast agents.

Table 1. **Physicochemical properties of selected ionic and non-ionic contrast agents**[16, 17]

	INN[a]	Iodine content at 300 mOsm/kg H_2O (mg I/mL)	Osmolality (mOsm/kg H_2O)	Viscosity[b] (mPa.s)
HOCM	**Ionic monomers** Diatrizoate (Reno-DIP®) Iothalamate (Conray®) Ioxithalamate (Telebrix®) Iodamide (Uromiro®) Metrizoate (Isopaque®)	~70	1 500 – 1 700	8 - 10
LOCM	**Ionic dimer** Ioxaglate (Hexabrix®)	~150	600	15.7
LOCM	**Non-ionic monomers** Iomeprol (Iomeron®) Iopentol (Imagopaque®) Iopamidol (Isovue®) Iopromide (Ultravist®) Iohexol (Omnipaque®) Ioversol (Optiray®) Ioxilan (Oxilan®) **Iobitridol (XENETIX®)**	~150	600 – 700	7.6 – 12
IOCM	**Non-ionic dimers** Iotrolan (Isovist®)[c] Iodixanol (Visipaque®)	~300	280	18.9 – 25.5

[a] INN (International Non Proprietary Names) may differ by country; not all agents may be approved locally
[b] Values are for ionic monomers at 300 mg I/mL, ionic dimer at 320 mg I/mL (20°C), non-ionic monomers at 300 mg I/mL (20°C) and non-ionic dimer at 320 mg I/mL (20°C).
[c] Not indicated for intravascular use.

Table 2. **Main adverse events of iodinated contrast agents**[3, 4]

Nausea	Nausea
Vomiting	Vomiting
Itching	Headache
Urticaria	Pruritus without urticaria
Angioedema	Maculopapular eruption
Pain on injection	Urticaria
Bronchospasm	Angioedema
Vasodilation	Iododerma
Tachycardia	Fixed drug eruptions
Hypotension	Erythema multiforme
Laryngeal oedema	Contrast - Induced Nephropathy
Cardiac arrest	
Pulmonary oedema	
Dyspnoea	
Arrhythmia	
Venous thrombosis	
Parotitis	
Exacerbation of thyrotoxicosis	

[a] Occurring 3 hours to 7 days after administration of contrast agent

The development of new contrast agents focused on reducing the osmolality of the solution, saving hydrophilicity and solubility by adding hydroxyl radicals [18] in order to reduce the occurrence of adverse events [19]. This was achieved during the 1970s with the initial introduction of an ionic dimer (**HEXABRIX®**) and the first non-ionic molecules (Table 1), which do not dissociate in water [13]. Ionic dimers at a concentration of 300 mg I/mL have an osmolality almost twice that of blood, lower than that of HOCM, and similar to that of non-ionic monomers [13]. These types of molecules with lower osmolality than HOCM became known as low-osmolar contrast agents (LOCM), amongst which **XENETIX®** is one of the most recent [20]. In a review of ionic versus non-ionic contrast agents studies, the incidence of adverse events with HOCM (i.e. ionic agents) was 3.8–12.7% compared with 0.6–3.1% with non-ionic LOCM [21]. Serious adverse events are rare, occurring in 1 to 6 per 1,000 examinations when HOCM are used but only in 1 or 2 per 10,000 examinations with LOCM [4, 16]. Subsequent development of contrast agents with an even lower osmolality saw the introduction of dimeric non-ionic molecules, with an osmolality equal to that of blood (i.e. iso-osmolar contrast agents (IOCM)) [13]. However, these dimeric molecules have a higher viscosity than monomeric agents. When osmolality is reduced, viscosity increases (although the relationship is not linear, as discussed in Section 2.4 «Osmolality» part), thus IOCM have a higher viscosity than LOCM, as shown in Table 1. Vascular resistance depends on fluid viscosity, not osmolality (Poiseuille's law). Indeed, there is experimental evidence that would support the notion that LOCM are superior to IOCM in preventing contrast agent-induced nephropathy [22]. Amongst the most common side effets of contrast agents are hypersensitivity reactions (Table 3) and contrast-induced nephropathy (Table 6) [22].

Table 3. Grading of immediate hypersensitivity reactions according to severity of clinical symptoms [16]

	Symptoms			
Grade	**Skin**	**Abdomen**	**Respiratory tract**	**Cardovascular system**
I	Pruritus, flush, urticaria, angio-œdema			
II	Pruritus, flush, urticaria, angio-œdema (not mandatory)	Nausea, cramping	Rhinorrhea, hoarseness, dyspnoea	Tachycardia (>20 beats/mn), BP change (>20mmHg systolic), arrhythmia
III	Pruritus, flush, urticaria, angio-œdema (not mandatory)	Vomiting, defecation, diarrhoea	Laryngeal œdema, bronchospasm, cyanosis	Shock
IV	Pruritus, flush, urticaria, angio-œdema (not mandatory)	Vomiting, defecation, diarrhoea	Respiratory arrest	Cardiac arrest

In clinical practice, pre-existing or contrast agent induced renal impairment is assessed by calculation of creatinine clearance according to the formula of Cockcroft and Gault [23] or to the simplified formula of MDRD (Modification of Diet in Renal Disease) [24], in adults (Table 4).

These two formula take into account four parameters to estimate the creatinine clearance:

- Sex
- Age
- Weight for the formula of Cockcroft and Gault or ethnic origin for the formula of MDRD.

Table 4. Equations to predict GFR in adults [23, 24]

	Formula	Constants
Formula of Cockcroft and Gault [23]	$eGFR = \frac{[140 - age] \times Bodyweight\ (Kg)}{S_{cr}} \times K$	K = 1.25 (male) K = 1.08 (female)
Formula simplified of MDRD (in males) [24]	$eGFR = 186 \times [S_{cr} \times 0.0113]^{-1.154} \times age^{-0.203} \times K$	K = 1.21 for African American patients K = 0.742 for females K = 0.95 if the serum creatinine level has been standardized to ID-MS (Isotope Dilution Mass Spectrometry)

eGFR = estimated glomerular filtration rate (mL/min); S_{cr} = Serum Creatinine (µmol/L)

In children, the formula of Schwartz [25] is the most adapted to young patients (between 6 months and 20 years) to estimate the creatinine clearance (Table 5).

Table 5. Equation to predict GFR in children [25]

	Formula	Constants
Formula of Schwartz [25]	$eGFR = \frac{[K \times Height\ (cm)]}{S_{cr}}$	K = 29 for new born K = 40 for infant K = 49 for children (less than 12 years old) K = 62 for boys (12-21 years old) K = 53 for girls (12-21 years old)

eGFR = estimated glomerular filtration rate (mL/min); S_{cr} = Serum Creatinine (µmol/L)

Table 6. ESUR Guidelines on prevention of contrast-induced nephropathy[26]

Renal adverse reactions to iodinated contrast media	
Definition	**Post-contrast acute kidney injury (PC_AKI)** is defined as an increase in serum creatinine ? 0.3 mg/dl (or ? 26.5 µmol/l), or ? 1.5 times baseline, within 48-72 hours of intravascular administration of a contrast agent. **Intra-arterial injection with first pass renal exposure** indicates that contrast agent reaches the renal arteries in a relatively undiluted form, e.g. injection into the left heart, thoracic and suprarenal abdominal aorta or the renal arteries. **Intra-arterial injection with second pass renal exposure** indicates that contrast agent reaches the renal arteries after dilution either in the pulmonary or peripheral circulation, e.g. injection into the right heart, pulmonary artery, carotid, subclavian, coronary, mesenteric or infra-renal arteries.
Risk factors for contrast medium induced nephropathy	
Patient related	■ eGFR less than 45 ml/min/1.73 m^2 before intra-arterial contrast medium administration with first pass renal exposure or in ICU patients. ■ eGFR less than 30 ml/min/1.73 m^2 before intravenous contrast medium or intra-arterial contrast medium administration with second pass renal exposure. ■ Known or suspected acute renal failure.
Contrast medium	■ Intra-arterial contrast medium administration with first pass renal exposure. ■ Large doses of contrast medium given intra-arterially with first pass renal exposure. ■ High-osmolality contrast media. ■ Multiple contrast medium injections within 48-72 hours.
Time of referral	
Elective examination	
Measure eGFR before administering intravascular iodine-based contrast medium	■ Either ■ (a) In all patients or ■ (b) In patients who have a history of - Renal disease (eGFR < 60 ml/min/1.73 m^2) - Kidney surgery - Proteinuria - Hypertension - Hyperuricemia - Diabetes mellitus **Timing of eGFR measurement** - Within 7 days before contrast medium administration in patients with an acute disease, an acute deterioration of a chronic disease or who are hospital inpatients. - Within 3 months before contrast medium administration in all other patients.
Emergency examination	
Identify at-risk patients (see above) if possible	■ Determine eGFR if the procedure can be deferred until the result is available without harm to the patient. ■ If eGFR cannot be obtained, follow the protocols for patients with eGFR less than 45 ml/min/1.73 m^2 for intra-arterial administration with first pass renal exposure and eGFR less than 30 ml/min/1.73 m^2 for intravenous administration and intra-arterial administration with second pass renal exposure as closely as clinical circumstances permit.

Before the examination	
Elective examination	
At-risk patients (see above)	■ Consider an alternative imaging method not using iodine-based contrast media. ■ Intravenous saline and bicarbonate protocols have similar efficacy for preventive hydration. ■ For intravenous contrast medium and intra-arterial contrast medium administration with second pass renal exposure hydrate the patient either (a) with intravenous sodium bicarbonate 1.4 % (or 154 mmol/l in dextrose 5 % water): 3 ml/kg/h for 1 hour before contrast medium or (b) with intravenous saline 0.9 % 1 ml/kg/hr for 3-4 hours before and 4-6 hours after contrast medium. ■ For intra-arterial contrast medium administration with first pass renal exposure hydrate the patient either with (a) intravenous sodium bicarbonate 1.4 % (or 154 mmol/l in dextrose 5 % water): 3 ml/kg/h for 1 hour before followed by 1 ml/kg/hr for 4-6 hours after contrast medium or (b) with intravenous saline 0.9 % for 3-4 hours before and 4-6 hours after contrast medium. ■ The clinician responsible for patient care should individualize preventive hydration in patients with severe congestive heart failure (NYHA grade 3-4) or patients with end-stage renal failure (eGFR < 15 ml/min/1.73 m^2). ■ Oral hydration is not recommended as the sole method of preventive hydration.
Emergency examination	
At-risk patients (see above)	■ Consider an alternative imaging method not using iodine-based contrast media. ■ Use preventive hydration before contrast medium administration (see 'Elective examination' for protocols).
Time of examination	
All patients	■ Use low- or iso-osmolar contrast media. ■ Use the lowest dose of contrast medium consistent with a diagnostic result. ■ For intra-arterial contrast medium administration with first pass renal exposure, keep either the ratio CM dose (in gram I) / absolute eGFR (in ml/min) < 1.1 or the ratio CM volume (in ml) / eGFR (in ml/min/1.73 m^2) < 3.0, when using contrast medium concentration of 350 mgI/ml.
After the examination	
At-risk patients	■ Continue preventive hydration if appropriate (see protocols above). ■ Determine eGFR 48 hours after contrast medium administration. ■ If at 48 hours there is a diagnosis of PC-AKI, monitor the patient clinically for at least 30 days and determine eGFR at regular intervals.

Note: No pharmacological prophylaxis (with statins, renal vasodilators, receptor antagonists of endogenous vasoactive mediators or cytoprotective drugs) has been shown to offer consistent protection against PC-AKI.

In conclusion, since the widespread use of LOCM, the frequency of adverse events has decreased considerably [4]. The majority of these are of mild severity and are non-life-threatening. Severe adverse events may be potentially or immediately life-threatening but are rare [4].

2. XenetiX®: an optimal combination

XENETIX® is one of the latest developed non-ionic iodinated monomers for radiological examinations (Table 1). In this **XENETIX®** monograph, an overview of the characteristics, posology and presentation of this contrast agent is followed by a review of its physicochemical, pharmacokinetic, toxicological and pharmacological profile. Thereafter, an in-depth review of the clinical safety and diagnostic efficacy of **XENETIX®** in patients undergoing a wide variety of radiological examinations is provided.

2.1 Product profile

XENETIX® is a non-ionic monomeric, iodinated contrast agent associated with high and stabilized hydrophilicity, low osmolality, low viscosity and high water-solubility. It is used in radiological examinations, and particularly in CT.

XENETIX® is supplied in 3 different concentrations: 250, 300 and 350 mg I/mL.

XENETIX® is approved for use in adults and children in a wide range of indications (Table 7), including intravenous (IV) urography, head and whole body CT and IA or IV digital subtraction angiography (DSA) and can be used via several routes of administration; local prescribing information should be consulted.

XENETIX® is approved in more than 60 countries.

2.2 Indications

Table 7. XENETIX® (iobitridol) indications [27–29]

	Intravascular administration		Local administration
	Intravenous route	**Intra-arterial route**	
XENETIX® 350	■ Intravenous urography ■ Head and whole body computed tomography ■ Intravenous digital subtraction angiography ■ Intravenous urography	■ Arteriography of all regions ■ Cardiac angiography	
XENETIX® 300	■ Head and whole body computed tomography ■ Intravenous digital subtraction angiography	■ Arteriography of all regions ■ Cardiac angiography	■ Endoscopic retrograde cholangiopancreatography ■ Arthrography ■ Hysterosalpingography
XENETIX® 250	■ Venography ■ Head and whole body computed tomography	■ Intra-arterial digital subtraction angiography	■ Endoscopic retrograde cholangiopancreatography

Not all the indications may be available in your country.
Please check with your local Guerbet representative for more information.

2.3 Presentation

XENETIX® is a clear, colourless to pale yellow, sterile, pyrogen-free solution for injection available in three concentrations (Table 8). Different volumes are supplied, allowing the exact volume to be specifically adapted to the individual patient and examination type.
Excipients of **XENETIX®** are: sodium calcium edetate (chelating agent), trometamol and trometamol hydrochloride (pH buffer), sodium hydroxide or hydrochloric acid, and water. Its shelf-life is 3 years [27-29].

XENETIX® is available in two delivery systems: glass vials/bottles and **ScanBag®**, which is a polypropylene bag based on IV infusion bag concept [30].

Table 8. XENETIX® (iobitridol) iodine content [27-29]

	Iobitridol	Corresponding to
XENETIX® 250[27]	54.84 g	25 g of iodine per 100 mL
XENETIX® 300[28]	65.81 g	30 g of iodine per 100 mL
XENETIX® 350[29]	76.78 g	35 g of iodine per 100 mL

Vials*

XENETIX® is packaged in type II glass vials/bottles with chlorobutyl rubber stoppers in the following volumes (Figure 1).

- **XENETIX®** 250: 100 mL
- **XENETIX®** 300: 20, 50, 75, 100, 150, 200 and 500 mL
- **XENETIX®** 350: 20, 50, 75, 100, 150, 200 and 500 mL

The vials/bottles should be stored below 30°C and protected from light [27-29].

XENETIX® optimizes handling with its integrated hanger label, available on 100, 150 and 200 mL containers.
The hanger does not occupy any space or interfere when not in use. Made of the same material as the label, the hanger simplifies discarding.

Figure 1. XENETIX® 350 iodinated contrast agent in vials with «integrated hanger label»

*Not all the presentations may be available in your country.
Please check with your local Guerbet representative for more information.

ScanBag®

ScanBag® is the first bag developed specifically for medical imaging, providing an innovative delivery method with the following advantages:

It is soft, light, resistant to tears and breakages, simple to use, safe to handle, practical and designed to achieve maximum sterility [30].
It also reduces storage and space wastage, assures transport safety and is compatible with most of the marketed automatic injectors.

Bags and tubing are composed of polypropylene (PP) and are, therefore, polyvinyl chloride (PVC), latex- and DEHP (di(2-ethylhexyl)phthalate)-free [31] and thus medically and ecologically safe as discussed below.

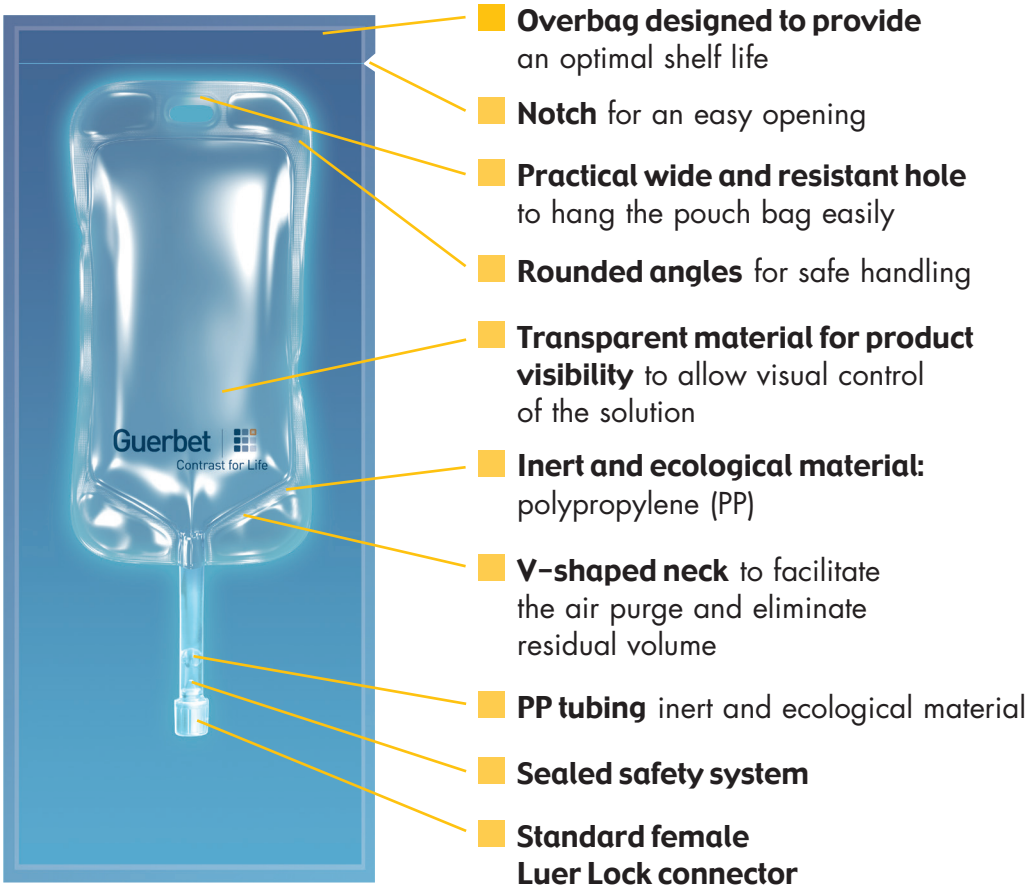


Figure 2. Features and advantages of ScanBag®

Innovative design to meet the requirements of medical imaging [28–30]

Figure 2 highlights the key features of **ScanBag®**, with every aspect focused on simplifying its use and meeting the latest requirements of medical imaging.
The shelf-life of **XENETIX®** stored in **ScanBag®** is the same as when stored in glass vials/bottles.

The bags should be kept in their outer carton to protect them from light.

XENETIX® 300 or 350 in **ScanBag®** is available in the following volumes: 100, 150, 200 and 500 mL*.

Inert material safe for the solution and for the patient

There are several medical safety advantages of the PP delivery system for medical agents:

- PP is an inert material
- PP is compatible with tested contrast agents
- There is no DEHP exposure. The United States Food and Drug Administration recommends limiting exposure to DEHP in at-risk populations (male fœtus, male neonate and peripubertal male) [31].
- There is no exposure to latex, a known allergen [32].

Packaging designed to simplify its use [30]

ScanBag® takes up to 64% less space than a bottle of the same volume and saves 270% space compared to bottles, when discarded. **ScanBag®** reduces storage and space wastage [30].

Safe for the environment

ScanBag® by **XENETIX®** has less impact on the environment during the healthcare waste disposal process because it can be safely incinerated, releasing only carbon dioxide and water as by-products [30]. In contrast, halogenated plastics such as PVC cannot be disposed of by incineration because they release exhaust gases containing hydrochloric acid and dioxins [33]. The advantages linked to **ScanBag®** have been evaluated from an environmental and sustainable development perspective, in order to measure its impact on environment and on public health compared to the glass vial, on the basis of a recognized methodology, life cycle assessment (LCA) (Figure 3) [34]. The LCA used for this study is compliant with the ISO 14 040 standards, including the critical review by an independant expert, and is based on a comparison of the environmental impact of the 2 forms, **ScanBag®** and the glass vial at each stage of the life cycle.

The LCA of both types of packaging, glass bottle and **ScanBag®**, covered three main phases:

1) The manufacturing phase (manufacturing of raw materials and intermediate, filling & assembling of the components used for making the packaging),
2) The transportation phase (all transports during the life cycle of the packaging, from the manufacturing site to the waste disposal site),
3) The end-of-life phase of the packaging at the hospital [34].

*Not all the presentations may be available in your country.
Please check with your local Guerbet representative for more information.

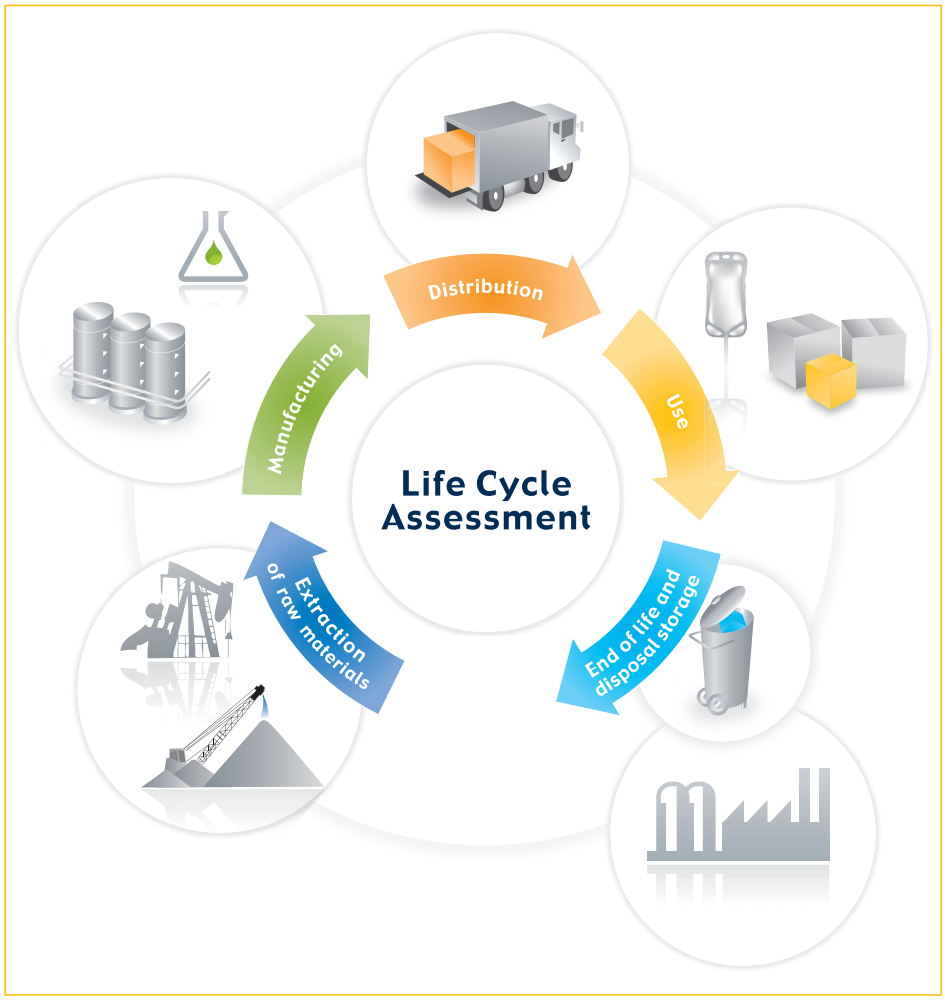


Figure 3. **Life Cycle Assessment (LCA)** [34]

Every stage, from manufacturing, transport to end of life of the packaging, was taken into account [34].

To evaluate the impact of both types of packaging on the environment and health, the environmental impact indicators studied were those defined in the selected LCA method (i.e., Institute of Environmental Sciences (CML) of Leiden University).

With **ScanBag®**, most of the environmental impacts (9 out of 11) are reduced by 33% to 75% (Figure 4, Table 9).

ScanBag® is less favourable compared to glass bottle regarding the freshwater aquatic ecotoxicity, mainly due to higher quantities of specific chemical components which are released from **ScanBag®** during the end-of-life phase.

The World Health Organization states that PVC-free plastics are preferable because of the reduction in toxic waste associated with their disposal [33].
ScanBag® complies with today's economical and environmental concerns.

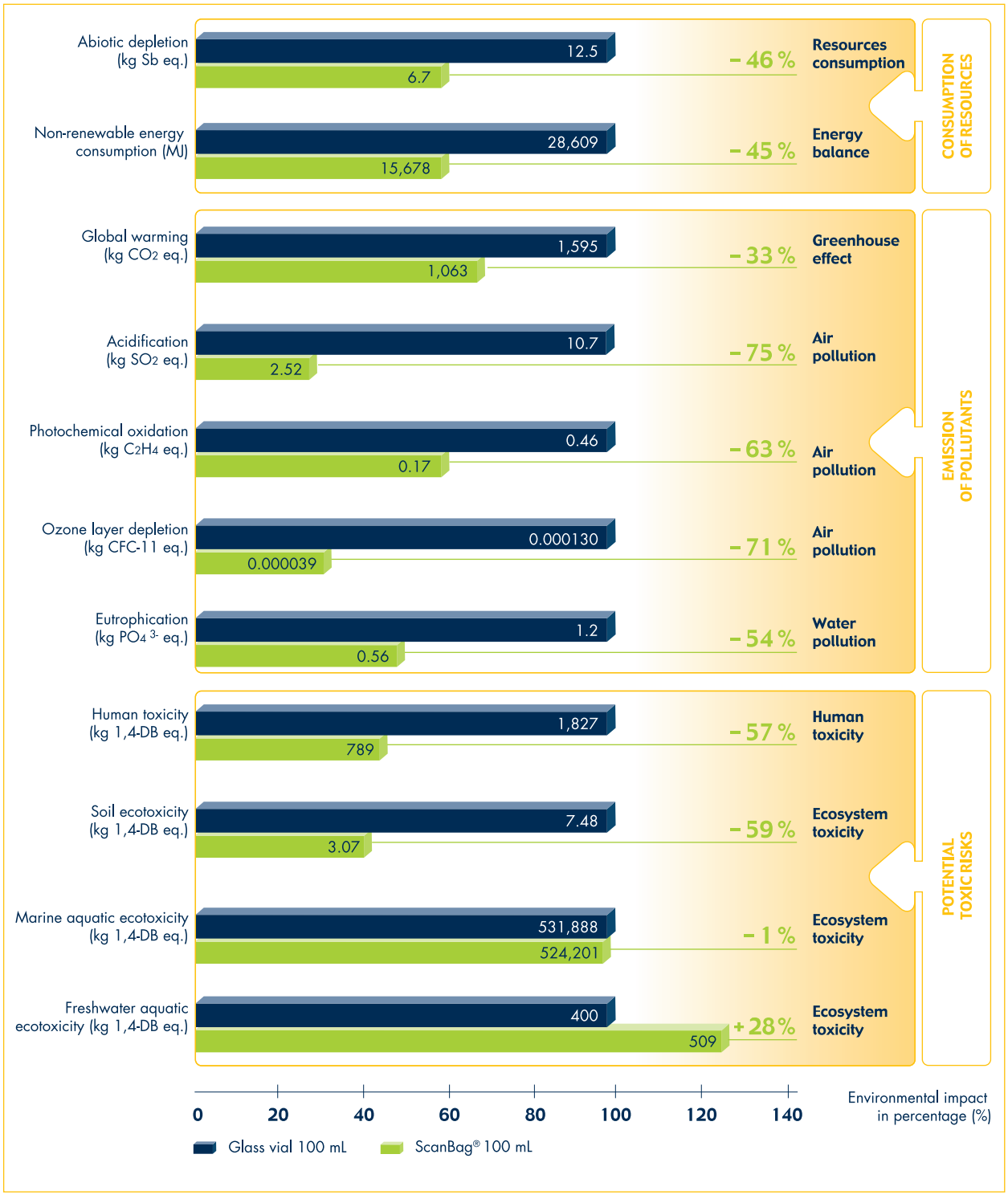


Figure 4. Comparative analysis between glass vial and ScanBag® on the environmental impacts [34]

Table 9. **Definitions of the environmental impact indicators selected for the Life Cycle Assessment of ScanBag® [34]**

	Environmental impact indicator	Definition	Measurement
CONSUMPTION OF RESOURCES	Abiotic depletion (Refers to the resources consumption)	This indicator characterizes the extraction of natural resources (including energy resources) considered as non-renewable, which are consumed at a speed greater than the time necessary for them to be produced naturally.	In kilograms of antimony per functional unit (kg Sb equivalent).
	Non-renewable energy consumption (Refers to the energy balance)	This indicator characterizes the sum of all sources of energy which are directly drawn from the fossil nature reserves (such as gas, petroleum, coal or nuclear).	In mega joules per functional unit (MJ).
EMISSION OF POLLUTANTS	Global warming or climate change potential (Refers to the greenhouse effect)	This indicator characterizes the mean atmospheric increase in substances of human origin such as carbon dioxide (CO_2), methane (CH_4) or nitrous oxide (N_2O). These emissions disturb the atmospheric balance and contribute to global warming. Climate change is a direct consequence of these phenomena.	In kilograms of carbon dioxide per functional unit (kg CO_2 equivalent).
	Acidification of air (Refers to the air pollution)	This indicator characterizes the increase in content of acidifying substances in the lower atmosphere that are responsible for acid rain and the dieback of forests.	In kilograms of sulphur dioxide per functional unit (kg SO_2 equivalent).
	Photochemical oxidation or smog (Refers to the air pollution)	This indicator characterizes the phenomena that lead to the formation of ozone and other oxidizing precursor compounds of ozone in the lower atmospheric layer. The ozone formed at this level has harmful effects on human and plant life.	In kilograms of acetylene per functional unit (kg C_2H_4 equivalent).
	Ozone layer depletion (Refers to the air pollution)	This indicator characterizes the thinning of the ozone layer, which leads to less efficient filtering of ultraviolet (UV) rays.	In kilograms of chlorofluorocarbon per functional unit (kg CFC-11 equivalent).
	Eutrophication or water pollution by nutriment excess (Refers to the water pollution)	This indicator characterizes the introduction of nutriments in the environment in the form of nitrogen or phosphate compounds disturbing ecosystems by promoting the proliferation of certain species (algae). The consequence is a reduction in the oxygen content of the aquatic environment, with repercussions on the flora and fauna.	In kilograms of phosphate per functional unit (kg PO_4^{3-} equivalent).
POTENTIAL TOXIC RISKS	Human toxicity (Refers to the potential impact on human health)	This indicator characterizes the theoretical capacity for intoxication of humans by various chemical components. This indicator does not measure damage caused but rather the risk of toxicity caused by emissions (in soil, air, water).	In kilograms of 1-4, dichlorobenzene per functional unit (kg 1,4-DB equivalent).
	Ecosystem toxicity (Refers to the potential impact on ecosystems through three dimensions: soil ecotoxicity, marine aquatic ecotoxicity and freshwater aquatic ecotoxicity)	This indicator characterizes the theoretical capacity for intoxication of different ecosystems (soil, marine water, freshwater) by various chemical components. This indicator does not measure damage caused but rather the risk of toxicity caused by emissions (in soil, air, water).	In kilograms of 1-4, dichlorobenzene per functional unit (kg 1,4-DB equivalent).

2.4 Physicochemical properties

The active ingredient of **XENETIX®** is iobitridol (molecular formula $C_{20}H_{28}I_3N_3O_9$ and molecular weight 835 g)[35]. Each molecule has three iodine atoms bound to a single benzene ring. As discussed previously, iodine provides the radiopaque property of iodinated contrast agents. The triiodinated benzene ring of iobitridol also has two tertiary amide groups and six hydroxyl groups[36].

The chemical structure of **XENETIX®** is 5-(3-hydroxy-2-hydroxymethyl-propionamido)-N,N'-dimethyl-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophtalamide[35] (Figure 5).

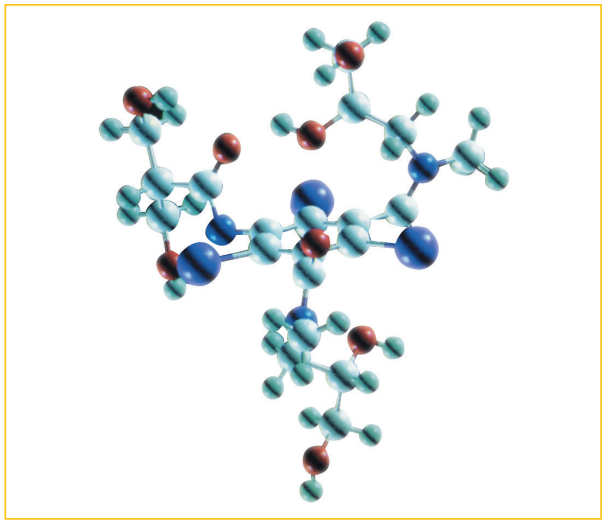


Figure 5. Structural formula of XENETIX® (iobitridol)

The physicochemical properties of **XENETIX®**, determine its efficacy and safety as with all

Hydrophilicity concept

Iodinated contrast agents can cause adverse reactions, such as hypersensitivity reactions, because of their chemotoxicity, which is related to their chemical structure[10]. By definition, chemotoxicity is described as interaction between the molecule of the contrast agent and proteins in the plasma or in biological membranes[10]. This interaction is hydrophobic in nature, and the capacity of an iodinated contrast agent to establish this molecular interaction with biological sites depends on the three-dimensional accessibility to these sites of the tri-iodinated benzene ring, and more specifically, to the lipophilic iodine atoms therein[20] (Figure 6).

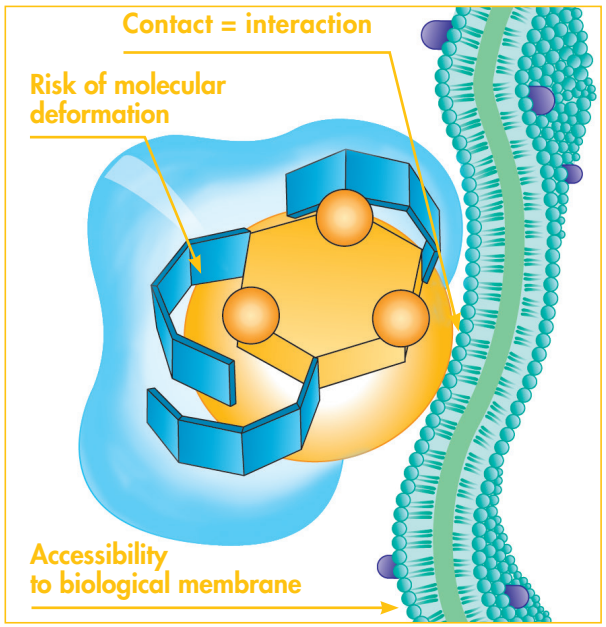


Figure 6. Risk of deformation of an iodinated contrast agent in the presence of a biological membrane

Quantitative hydrophilicity

Chemotoxicity decreases as the number of hydroxyl groups in the molecule increases and the number of carboxyl molecules decreases [10]. Therefore, with no carboxyl groups and a high number of hydroxyl groups (six per molecule) **XENETIX®** has a low potential for chemotoxicity; its physicochemical properties make it a stable product (Table 10).
Compared to the other LOCM and IOCM, **XENETIX®** has one of the highest numbers of OH radicals, which is expected to improve the protection of biological membranes.

Table 10. Number of hydroxyl groups in selected non-ionic contrast agents

Number of OH	INN[a]
4 OH	Iopromide (Ultravist®)
5 OH	Iomeprol (Iomeron®) Iopentol (Imagopaque®) Iopamidol (Isovue®)
6 OH	Iohexol (Omnipaque®) Ioversol (Optiray®) **Iobitridol (XENETIX®)**
9 OH	Iodixanol (Visipaque®)

[a] INN = International Non Proprietary Names may differ by country; not all agents may be approved locally

Qualitative hydrophilicity

Qualitative hydrophilicity refers to the creation with hydroxyl groups of a hydrophilic zone that masks the inner lipophilic (i.e. hydrophobic) benzene ring, thus potentially preventing interaction between this ring and cellular proteins [18].

One of the measures of a molecule's relative hydrophilicity is its octanol/water partition coefficient [18]; this coefficient is calculated as Log P = log of the percentage of distribution of a molecule between an organic (octanol) and an aqueous phase. The value –2.70 for **XENETIX®** [20], is amongst the highest compared with other non-ionic monomers (–3.57 for ioversol, –2.85 for iohexol, –2.58 for iopamidol, –2.43 for iopentol and –2.35 for iopromide) [37].

However, the partition coefficient only partially explains the potential for interaction with biologic proteins [18]. The position of the hydroxyl molecules relative to the hydrophobic benzene ring is also important [18]. **XENETIX®** has an even distribution of the six hydroxyl groups, giving it an evenly distributed facial hydrophilicity and consequently minimizing the accessibility of the inner lipophilic areas to biologic proteins [38].

Stabilized hydrophilicity

Additionally, because there is a risk of molecular deformation by hydrophobic forces when a contrast agent molecule comes into contact with proteins or biological membranes (Figure 6) [39], **XENETIX®** was designed to be a more rigid, stabilized molecule (Figure 7), by increasing the length of the branched side chains [39] and through the binding of the methyl (CH_3) groups of two tertiary amide groups; this stability was confirmed in a study of **XENETIX®** stereo-isomers [20, 36].

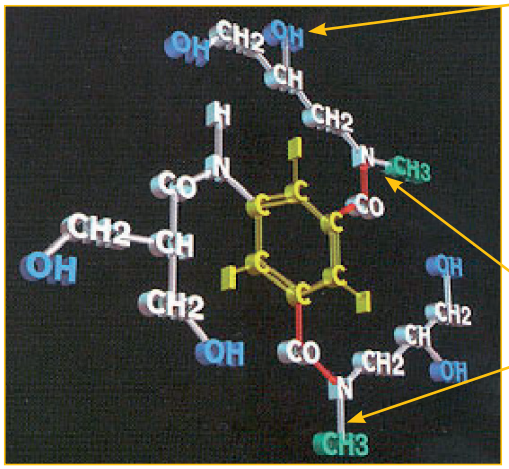


Figure 7. Representation of the stabilized hydrophilicity of XENETIX®

Biological relevance of the stabilized hydrophilicity

An x-ray diffraction study of the complex formed between **XENETIX®** and pancreatic porcine elastase showed that **XENETIX®** does not interact with the active site of this enzyme, unlike another non-ionic monomer iohexol. This study supported the concept of «hydrophobic shielding» which was at the origin of the design of **XENETIX®** [39].

Water-soluble iodinated contrast agents are excreted unmetabolized by the kidney [14]; however, very small amounts may be taken up by renal tubular epithelial cells [40]. In another study, although iohexol (a non-ionic monomer) and **XENETIX®** were taken up to a similar degree by renal proximal tubules after selective intra-renal injection to uninephrectomized rats, **XENETIX®** was eliminated by the lysosome/vacuole system more rapidly than iohexol, so that, at 24 hours after perfusion, intracellular iodine concentrations were lower in **XENETIX®** than in iohexol-exposed rats [40]. These observations might be explained by the stabilized hydrophilicity of **XENETIX®**.

In conclusion, given the quantitative, qualitative and most importantly the stabilized hydrophilicity of **XENETIX®**, the risk of contrast agents reactions due to interaction between the iodinated benzene ring of the molecular and biologic proteins is considered to be low.

Osmolality

Osmolality of a contrast agent solution refers to its ability to induce the movement of water across biological membranes and is determined by the ratio of the number of iodine atoms to the number of particles in solution [10]. The intravascular administration of iodinated contrast agents transiently raises the osmolality of the plasma, which results in tissue fluid being attracted by osmosis from the extravascular compartment into the blood. Osmotoxic effects include transient pain following intra-arterial injection, erythrocyte shrinkage and haemodynamic effects such as transient vasodilatation and hypervolaemia. Indeed, the administration of HOCM actually reduces the systemic peripheral resistance and consequently lowers blood pressure [41].

In contrast to HOCM, **XENETIX®**, like other LOCM, has a higher ratio of iodine to active particle (3:1 in solution) and thus a lower osmolality (Table 1).

Other agents with even lower osmolality than LOCM are the IOCM, (non-ionic dimers) that are iso-osmolar with plasma[14] but may still cause osmotic diuresis [10].

As shown by Schnermann and Briggs, the osmolality does not directly affect the tubuloglomerular feedback. Thus, perhaps too much attention has been directed to osmolality, while neglecting the impact of other physicochemical properties. There is an exponential relationship between concentration and viscosity [22].

Viscosity

The viscosity of **XENETIX®** and other contrast agents varies with temperature and iodine concentration. Generally an increase in temperature leads to a decrease in viscosity (Table 11) [27-29].

Intravenous injections, particularly at high flow rates, are more difficult if the contrast agent has a higher viscosity [13].

Apart from this procedural concern, there are safety concerns relating to the viscosity of contrast agents; it has been proposed that viscosity of contrast agents, independent of their other properties, may have a deleterious effect on renal haemodynamics [42] (Figure 8).

The viscosity of **XENETIX®** is the same as that of iohexol (Table 1) and lower than that of non-ionic dimers at the same temperature (20°C) and iodine concentration (300 mg of iodine per mL [mg I/mL]).

XENETIX® = 11 mPa.s, iohexol = 11.6 mPa.s, iopentol = 13.2 mPa.s and iodixanol = 18.9 mPa.s [43, 44].

Table 11. Summary of the physicochemical properties of XENETIX® (iobitridol) [27–29]

Osmolality and viscosity values according to iodine concentration			
	Osmolality (mOsm/kg H_2O)	Viscosity (mPa.s) at 20°C	at 37°C
XENETIX® 250	585	6	4
XENETIX® 300	695	11	6
XENETIX® 350	915	21	10

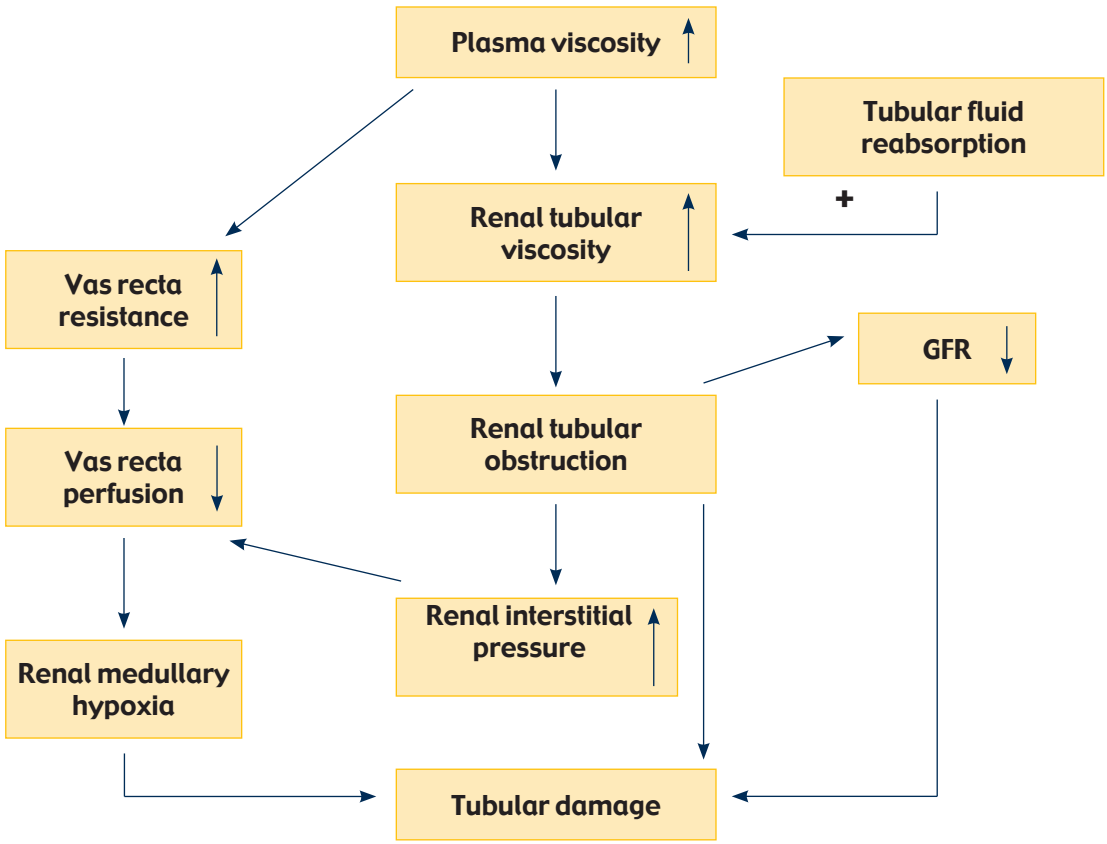


Figure 8. Flow chart of mechanisms linking fluid osmolality to renal damage [22]
GFR is glomerular filtration rate.

Solubility

Solubility is determined by the number of hydroxyl groups in the molecule and is related to hydrophilicity (see section 2.4, «Stabilized hydrophilicity» part). **XENETIX®** has good solubility because of its even and stable distribution of six hydroxyl groups. When cold, the solubility of **XENETIX®** is greater than 140% (mass/ volume) [36].

2.5 Pharmacokinetics

The pharmacokinetic profile of **XENETIX®** is consistent with that of other iodinated contrast agents, i.e. it behaves as a marker of extracellular fluid [45], with very low plasma albumin protein binding (2.1%) [45] and elimination mainly via the renal route [27-29].

Biodistribution

After intravascular administration, **XENETIX®** is distributed rapidly in the vascular compartment and then diffuses into the interstitial compartment, according to an in vivo study of the biodistribution and efficacy of **XENETIX®** during CT examinations in rabbits. In this study, the pharmokinetic behaviour of **XENETIX®** was similar to that of iohexol. CT images revealed that immediately after injection of **XENETIX®** there was an early increase in density (i.e. image enhancement) in the aorta, followed by a rapid decrease. Thereafter there was rapid hepatic enhancement which then decreased linearly over time; opacification of the renal excretory activities indicated normal renal elimination [46].

In vivo studies show that the pharmacokinetics of **XENETIX®** is linear between 300 and 1500 mg I/kg [45].

Two animal studies showed that **XENETIX®** does not cross the blood-brain barrier [47, 48]. As with other non-ionic monomers, a radioactive labelling study in rats showed uptake of injected iodine in the thyroid after **XENETIX®** administration [47].

Elimination

XENETIX® is rapidly and almost completely eliminated by glomerular filtration, without tubular re-absorption or secretion, in unchanged form [27-29, 45]. In rats, the majority of the injected dose is detected in the urine 24 hours after injection (86.3%) with only 5.7% being excreted faecally [47]. Urinary and faecal elimination is complete by 24 hours post-dose [45]. In rats, the cumulative excretion 48 hours after administration of a single dose of **XENETIX®** 300 mg I/kg was 99–102% [47]. In rabbits and dogs, more than 90% of **XENETIX®** was eliminated in the urine within 4-5 hours, and biliary excretion was found to be very low [45].

In humans, the pharmacokinetics of **XENETIX®** was evaluated in 20 healthy subjects divided in four groups receiving either **XENETIX®** at a dose of 0.2 g I/kg, 0.4 g I/kg or 0.6 g I/kg or saline*. The elimination half-life is about 1.8 hours. **XENETIX®** is not metabolized. **XENETIX®** is dialysable [27-29].

* Data on file

Pregnancy or lactation in animals[49]

There is minimal transplacental passage of IV **XENETIX®** 300 mg I/kg from dam to fœtus in pregnant rabbits, with the concentration of **XENETIX®** in the foetal plasma and amniotic fluid below the limit of quantification.

There is almost no excretion of **XENETIX®** in the milk of lactating goats after IV injection of 300 mg I/kg; a mean of 0.7% of the administered dose was detected in the milk compared to 1.6% for iohexol[49].

In case of renal impairment[27-29]

The pharmacokinetics of **XENETIX®** in renal impairment has been studied in rats. Plasma clearance is decreased and biliary excretion increased (the latter from 0.4% to 9%) in rats with renal impairment compared with rats without renal impairment[51].

As with any water-soluble iodinated contrast agents, partial elimination of **XENETIX®** occurs via the biliary route in human subjects[50]. **XENETIX®** can be dialysed and is therefore suitable in patients receiving dialysis[27-29].

2.6 **Pre-clinical** toxico-pharmacology

The pharmacological profile of **XENETIX®** is generally similar to or better than that of other iodinated contrast agents[44]. Most pharmacological data reviewed in this section are from in vitro or animal studies.

IV use of **XENETIX®** does not demonstrate any particular toxicological effects according to findings from single- and multiple-dose toxicity studies in the rat and the dog. After oral administration to mice up to 17.5 g I/kg, no clinical signs, deaths, alterations in bodyweight were noted[52]. Iodinated contrast agents classically produce steep dose-effect (lethality) curves, which were also observed with **XENETIX®** and iohexol in single-dose animal toxicity studies (Table 12). In multiple-dose studies, there were no deaths in rats after 28 days of treatment with IV **XENETIX®** at 3.5 g I/kg/day or in dogs after 4 weeks at a dose of up to 2.8 g I/kg/day[52].

Table 12. Single-dose toxicity in mice of intravenous XENETIX® (iobitridol) versus intravenous iohexol administered at 2 mL/min. Adapted with permission from Donadieu et al.[52]

	XENETIX®	Iohexol
Iodine concentration (mg I/mL)	350	350
LD_{50} (g I/kg) in males	16.8	16.8
LD_{50} (g I/kg) in females	16.6	16.7

LD_{50} = lethal dose in 50% of tested animals

Renal effects

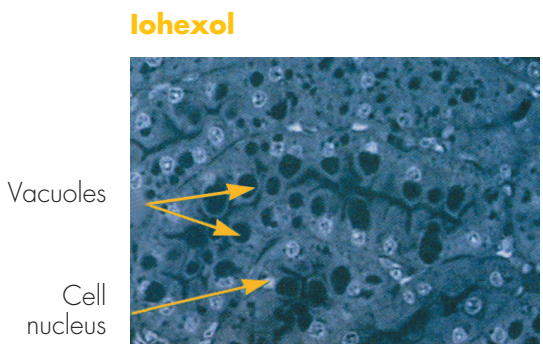
In the clinical setting, contrast agents may cause contrast-induced nephropathy (CIN) particularly in at-risk patients (pre-existing renal failure, diabetes mellitus, etc) [53]. The exact pathophysiology of CIN has not been clearly established but numerous pharmacological mechanisms have been proposed such as direct tubular toxicity or a reduction in renal perfusion (which leads to medullary hypoxia), all of which lead to a reduction in the glomerular filtration rate [53].

In addition to osmolality, viscosity may also play an important deleterious role in the occurrence of CIN. The viscosity of a contrast agent has an impact on urine flow and can lead to haemodynamic effects [42] (Figure 8).

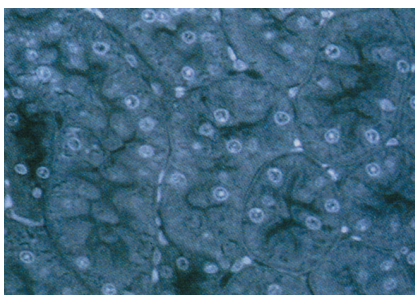
In vitro, **XENETIX®** inhibited accumulation of para-aminohippuric acid to a significantly lesser degree than iohexol, suggesting less tubular toxicity with **XENETIX®** [54]. Histological examination of the kidney of rats treated by selective injection or repeated IV injections showed that late vacuolization of renal tubular epithelial cells of the cortex was significantly less marked with **XENETIX®** than with iohexol [55, 56] (Figure 9).

XENETIX® was associated with similar or lesser renal effects compared with other iodinated contrast agents as shown in Table 13.

This may be because **XENETIX®** has a lower viscosity than some other agents [53] differences in viscosity, rather than osmolality alone, could explain the differences between iodinated CM in terms of effects on renal perfusion and tubular flow [53].



Vacuolization of proximal tubular cells (external cortex) after iohexol



Normal appearance of the outer cortex. No vacuolization of the proximal tubular cells after **XENETIX®**

Figure 9. Histological examination of the kidney of rats treated by CM injection [55]

Table 13. Summary of renal effects of XENETIX® (iobitridol)

	Comparative data	Study details
Renal blood flow:	XENETIX® = iohexol	IA administration in dogs [44]
transient ↑ then ↓	XENETIX® < iodixanol	IV administration in rats [58]
Medullary blood flow ↔	ioxaglate ≈ XENETIX® < iodixanol	IV administration
Cortical blood flow ↓↓	ioxaglate ≈ XENETIX® < iodixanol	in rats [59]
Urine output ↑	XENETIX® ≈ iohexol	IA administration
GFR ↔	XENETIX® < iohexol	in dogs [44]
Blood creatinine ↑	ioxaglate < iodixanol < XENETIX®	IV administration
	<iohexol < iomeprol < iopamidol < iopromide	in rabbits [60]
Creatinine clearance ↓	XENETIX® = iohexol = control	IA administration
Urinary NAG activity ↑	XENETIX® = iohexol	in rats [55]
Creatinine clearance ↓	XENETIX® = iohexol > control	Rat model of acute renal failure;
Urinary NAG activity ↑	XENETIX® = iohexol > control	IV administration [54]

GFR = glomerular filtration rate; IV = intravenous; NAG = N-acetyl-beta-D-glucosaminidase

↔ indicates no change/no effect; ↓ indicates decrease; ↑ indicates increase
≈ indicates similar effect; = indicates statistical analysis was done, but no significant difference was observed; > indicates greater effect; < indicates lesser effect

Reproduction

Given the fact that studies in rats and rabbits found no evidence of teratogenicity [52], there is no expectation that **XENETIX®** has teratogenic effects. No data are available regarding the effects of **XENETIX®** on reproductive function [27-29].

Mutagenesis

Although iodinated contrast agents are not known to be mutagenic, three in vitro tests and one in vivo (micronucleus test) were performed on **XENETIX®** in compliance with European requirements. No mutagenic effect was observed [27-29].

2.7 Pharmacological effects

The safety pharmacological profile of **XENETIX®** is generally found to be similar to or better than that of other iodinated contrast agents [44], based on in vitro or animal studies available.

Haemodynamic, cardiac and thrombotic effects

Haemodynamic parameters (such as blood pressure) can be altered by iodinated contrast agents because they induce an osmotic overload [10]. In interventional procedures, there is a risk of cardiac electrophysiological effects that may deteriorate into rare, but serious reactions such as ventricular fibrillation [57]. Thrombotic complications (acute thrombotic coronary occlusion) have been observed during diagnostic coronary arteriography, especially with non-ionic contrast agents [19].

XENETIX® has minor or transient effects on haemodynamic and cardiac parameters, than other iodinated contrast agents, and was not different from other non-ionic monomers in inducing ventricular fibrillation in in vitro and/or animal studies [44, 57, 58, 61].

Other effects

Iodinated contrast agents may cause both immediate and delayed hypersensitivity reactions [62, 63]. **XENETIX®** induced histamine release to a similar extent as ioxithalamate and iohexol, but to a significantly lesser extent than the non-ionic dimers (iotrolan and iodixanol), in an isolated guinea pig lung model perfused by autologous blood [64]. **XENETIX®** at a dosage of 1 and 5 mL/kg did not induce bronchospasm after IV injection in guinea pigs [44].

Another pharmacological effect of non-ionic contrast agents is echinocytosis [65]. **XENETIX®**causes echinocytosis to a significantly smaller degree than iopamidol, even though iopamidol has a lower osmolality [44]. Similarly, **XENETIX®** caused significantly ($p < 0.01$) less disturbance to external erythrocyte membrane fluidity than iohexol and iopamidol in another in vitro study using human red blood cells [66].

Finally, iodinated contrast agents may damage and then cross the blood-brain barrier, an effect proposed to be independent of their osmolality [67].

In an in vitro study of central nervous system (CNS) synaptic transmission using rat hippocampal slices, high concentrations of **XENETIX®** produced a transient excitatory response, followed by transient mild inhibitory effects, a biphasic action present in most of the other contrast agents examined (iomeprol, ioversol, iopentol, diatrizoate, ioxaglate) [68]. However, the significance of these data is not certain; in a study in rabbits, intra-carotid injection of **XENETIX®** during cerebral arteriography was not associated with any changes in EEG parameters, and was therefore not different from the control (a hypertonic solution of mannitol) [48].

3. Clinical safety of XENETIX®

XENETIX® is well tolerated and safe for use in patients of a wide range of ages, including patients with risk factors for reactions to contrast agents [69-72], although local clinical guidelines and the local Summary of Product Characteristics (SPC) should always be taken into account.

3.1 Post-marketing surveillance

Three pooled post-marketing surveillance studies (PMS) were conducted in a total of 163,786 patients aged between a few weeks and 101 years who received **XENETIX®** during CT (59% of patients), IV urography (35%), DSA (3%) or other examinations (e.g. venography, angiography; 3%) [69-72]. **XENETIX®** was given at a dose of 1 mL/kg body weight [71] or at a concentration of 300 mg I/mL in the majority of patients (94.8% [70] and 92.7% [69] respectively).

The majority (99%) of patients did not experience a product-related adverse event (Figure 10) [69-72].

Most adverse events were of minor severity and the most common were «feeling of warmth» (0.1–1.3%), nausea (0.24–0.3%) and urticaria (0.1–0.12%) [69-71]. Those regarded as serious were very rare [69-71]; anaphylactic shock occurred for one patient in one study [71], and in another study, dyspnoea (n = 17), hypotension (n = 4) and anaphylactic shock (n = 3) were reported [70]. Only one fatal event occurred: cardiac failure in a male patient who underwent CT with injection of 150mL of **XENETIX®**. He had a history of chronic obstructive pulmonary disease and respiratory insufficiency. He developed cyanosis and dyspnoea during the procedure with subsequent cardio-respiratory arrest [69], but whether his death was considered contrast agents-related was not stated.

In the Petersein et al. study, adverse events were observed in a total of 1,390 patients (2.3%). An association with **XENETIX®** was considered likely in 577 patients and was assumed in another 124 patients [69].

In the Vogl et al. study, adverse events were reported for less than 1% (502 patients out of 52,057). The causal relationship to **XENETIX®** was considered probable in 318 patients and possible in 57 patients [70].

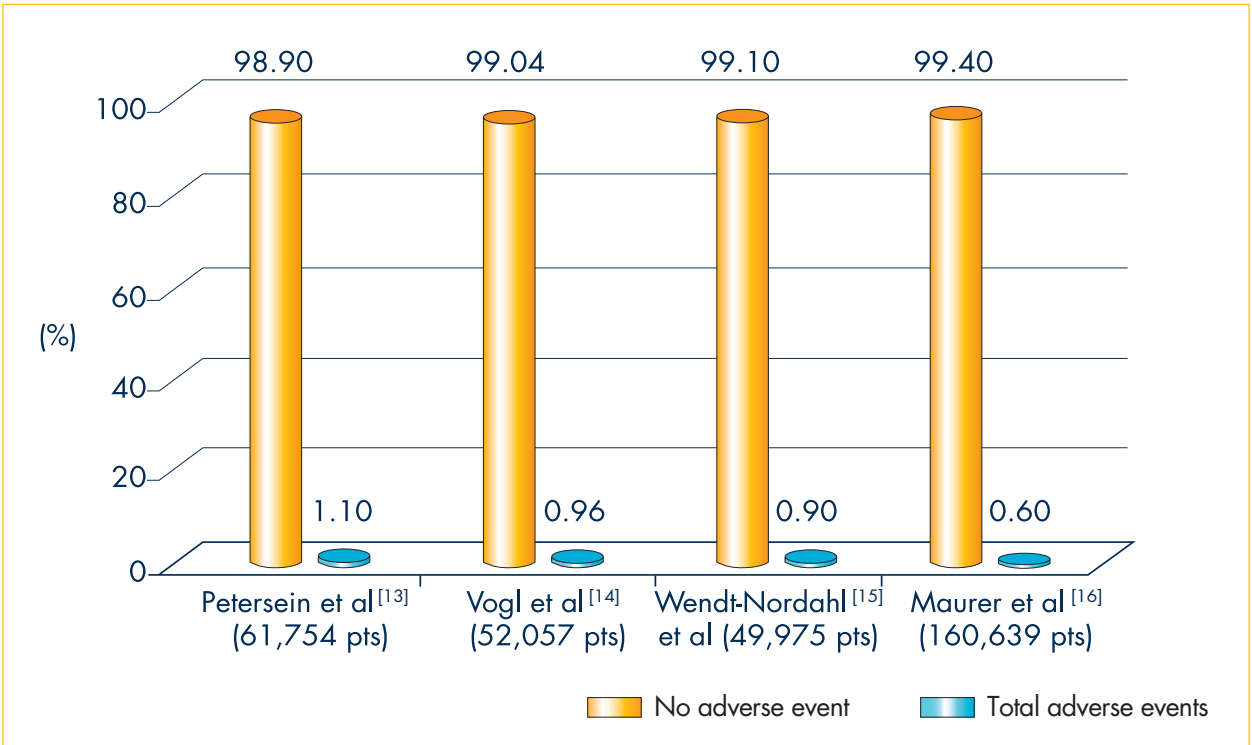


Figure 10. Safety profile of XENETIX® in four post-marketing surveillance studies [69–72]. Product-related adverse events are shown (data from Petersein et al. [69] does not include «feeling of warmth»)

Patients receiving a very small volume of contrast agent experienced a higher incidence of adverse events in two of these studies [69, 70].

For example, the adverse event rate was 6.13% in 359 examinations that used a volume of less than 50 mL compared with 0.83–1.23% in 49,755 examinations that used a volume ≥ 50 mL ($p < 0.001$) [70]. In this study, the lowest iodine concentration of **XENETIX®** 250 was associated with a significantly ($p < 0.001$) higher incidence of adverse events and serious adverse events than those receiving **XENETIX®** 300 or 350 [70], but this was attributed to a higher proportion of «at-risk» patients receiving this concentration (generally injected in conventional angiography).

It was also noted, in this and other studies, that the incidence of adverse events was significantly ($p \leq 0.05$) higher in female than male patients [70, 71]. This is consistent with the results of two large-scale studies [73, 74].

More recently, this good tolerance was confirmed in a PMS including 160,639 additional patients (general population and at-risk patients).[72]

In particular, 21.8% of all patients had at least one risk factor (renal impairment, hypo- or hypertension, diabetes mellitus, coronary heart disease), 7.3% were patients with allergies or who had previously reacted to contrast agent [72].

In 17,614 patients, the polypropylene infusion bag (**ScanBag®**) was used. The good efficacy of **XENETIX®** was confirmed, with diagnosis assessed possible in 99.5% of all cases, and image quality graded good or excellent in 92.2%.

Regardless of the container used (vials or **ScanBag®**), the good safety of **XENETIX®** was confirmed with a very low rate of 0.6% of total adverse events [72].

Overall, the four retrospective, post-marketing studies concluded that **XENETIX®** is well tolerated and safe to use.

3.2 Clinical studies

Comparative clinical trials were conducted to establish the tolerability profile relatively to other contrast agents. In most of these studies, adverse events were only assessed early after contrast media (CMs) administration (during and up to 30 minutes).

The safety of **XENETIX®** was compared with that of iopamidol [75-77], iopromide [76, 78, 79], ioxaglate [80], iomeprol [95] and iohexol [75, 78, 81-86] in clinical trials (see Tables 15, 17, 19, 21, 22 in section 4 «Diagnostic efficacy»). In most of these studies, adverse events were only assessed early after CM administration (during and up to 30 minutes after CM administration). Section 3.3 «Safety specificities» reviews a study that also investigated «late» adverse reactions [77].
A few of the comparative studies addressed safety specificities as follows (see also section 3.3):

- The degree of heat sensation assessed using a test-defined heat score was not different between **XENETIX®** 350 mg I/mL and iopamidol 340 mg I/mL in patients undergoing left ventriculography or aortography or both [77]. Data on ventricular fibrillation from this study are discussed in Section 3.3 «Cardiovascular and thrombotic safety» part.
- Neurosensory or nervous system disorders were very rare after administration of **XENETIX®** [27-29].
- In randomised, double-blind studies **XENETIX®** 350 mg I/mL had no clinically significant effect on laboratory or haematology parameters, and was generally not different from iohexol for these parameters, during coronary angiography and ventriculography [83] or head CT [82].

3.3 Safety specificities

Renal safety

In a retrospective study [87], **XENETIX®** 350 was well tolerated in patients with renal impairment and mild-to-moderate risk for CIN referred for coronary and/or peripheral procedures. Similar tolerance results were obtained in a small study in patients with renal impairment who underwent

a radiological procedure with (n=11) or without (n=10) administration of **XENETIX®** [88]. The value of a concurrent control group has been underlined. It allows to estimate the probability that the reported serum creatinine elevations after injection of contrast agents were, in fact, caused by contrast agents [89]. Renal impairment was defined as a serum creatinine level of ≥ 133 µmol/L (1.5 mg/dL) and/or an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73m^2 [87].

In these studies, there were no serious renal adverse events (i.e. need for dialysis) [87, 88, 90, 91].

In the retrospective study, **XENETIX®** was as well tolerated as iodixanol 320 mg I/mL when given with prophylactic IV saline (for hydration) plus N-acetylcysteine. There was no significant difference between groups in the incidence of CIN (3.5% of 115 patients vs. 2.7% of 110 patients) or in the change from baseline in renal function parameters at 48 hours, including serum creatinine levels (Figure 11). CIN was defined as an increase in the serum creatinine levels of ≥ 0.5 mg/dL (44.2 µmol/L) 48 hours after administration of the contrast agents. Additionally, in the subgroup of patients with diabetes, the renal tolerability of **XENETIX®** (n = 49) and iodixanol (n = 55) was similar; CIN occurred in 4.1% versus 5.5% of patients, respectively, and macroalbuminuria in 12% and 13% [87].

In a prospective study, in 222 patients with renal failure, who were undergoing a coronary procedure, iodixanol was used in 144 patients whereas non-ionic low osmolar agents were used in 78 patients (**XENETIX®** n = 30, iomeprol n = 40, iopentol n = 8). The CIN incidence was 14.6% for iodixanol versus 14.1% for non-ionic low osmolar agents (**XENETIX®**: 10%, iomeprol: 10% and iopentol: 50%) [90].

The good renal safety of **XENETIX®** has also been demonstrated in a comparative study (**XENETIX®** 300 / iodixanol 270) in a paediatric population. Despite its higher iodine concentration and osmolality, **XENETIX®** displays a similar renal safety profile based on creatinine clearance assessments without significant effects on CIN occurence [91] (see section 3.4 «Paediatric population» part, for more information).

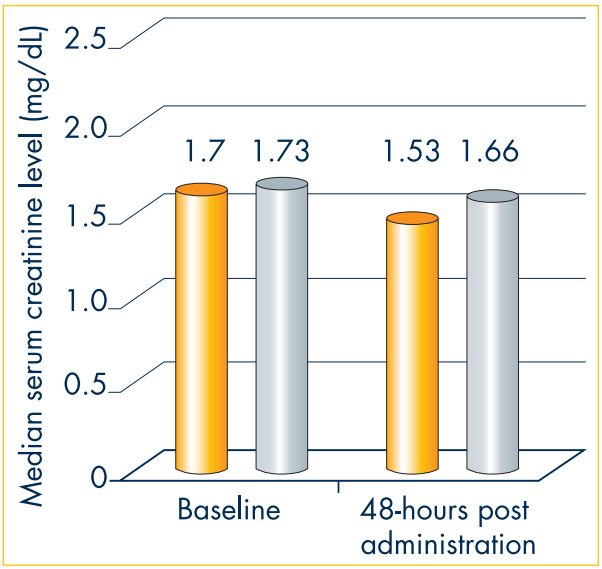


Figure 11. Change from baseline in serum creatinine levels with XENETIX® 350 and iodixanol 320 in patients with renal impairment having coronary and/or peripheral angiography and/or angioplasty (retrospective study) [87]

Hypersensitivity reactions

As any contrast agent, **XENETIX®** can cause hypersensitivity reactions (both immediate and delayed), but these are very rare (very rare defined as occurring in ≥ 0.01% and < 0.1% of patients) [27-29]. In general, immediate allergy-like reactions from iodinated contrast agents are of mild severity, transient and do not require treatment [3]. Severe immediate reactions are rare and occur less frequently with LOCM than HOCM [13].

Moreover, in three post-marketing surveillance studies, **XENETIX®** severe hypersensitivity reactions were rare as only five patients out of 163,786 had an anaphylactic shock. (one each in the Petersein et al. [69] and Wendt-Nordahl et al. [71] studies, and three in the Vogl et al. study [70]).

Delayed reactions to iodinated contrast agents are typically mild to moderate skin reactions [3]. A comparative study investigated «late» adverse events (i.e. occurring 1 week after discharge) and found that the incidence of most late adverse events such as skin rash, nausea, wheezing, face swelling, tongue swelling and «other symptoms» was similar between **XENETIX®** 350 and iopamidol 340 mg I/mL recipients after IV administration during cardiac catheterization [77]. However, overall, more **XENETIX®** than iopamidol recipients had late adverse events (18.5% of 638 vs. 13.9% of 732 patients; p = 0.02) [77]. This difference was mainly due to a difference in the incidence of «itching» (8.2% vs. 5%; p = 0.03), the clinical significance of which was not reported.

Importantly, such delayed skin reactions after administration of iodinated contrast agents do not usually require treatment and resolve spontaneously [3].

Patients with a previous adverse reaction to contrast agents and/or with asthma or allergies are considered at greater risk for experiencing an adverse reaction [3] (see also section 3.4, in «At-risk populations» part). **XENETIX®** is contraindicated in patients with hypersensitivity to **XENETIX®** or who have experienced a contrast agent-associated major immediate reaction or delayed skin reaction [27-29].

Allergic and various non-specific reactions

A recent study [92] retrospectively evaluated the incidence rates of immediate adverse drug reactions (ADRs) caused by four different low-osmolar non-ionic CMs used in computed tomography (CT) examinations at a single institute in South Korea.

Using the spontaneous reporting programme and clinical data repository system (CDRS), 1969 immediate ADRs from 286 087 examinations of 142 099 patients who performed contrasted CT examinations between January 2006 and December 2010 were enrolled in this study, and their medical records were reviewed.

Immediate ADR was defined as an adverse reaction that occurred within 1 h after administration of a CM. Immediate ADR included all allergic reactions and various non-specific reactions. Among the 1969 immediate ADRs, specific symptoms were recorded in 1910 ADRs.

Possible risk factors for immediate ADR were also examined. Examinations involving the following CMs were considered: **XENETIX®**, iohexol, iopamidol, and iopromide. Cases were grouped according to the frequency of CT examinations per day (single CT, multiple CT). Single CT refers to one CT examination per day, while multiple CT refers to more than one CT examination per day. Patient age, gender, and body weight were also taken into account in the analysis.

Table 14. Top ten symptoms of immediate ADRs

Symptom	n	%
Rash	1630	85.3
Itching sensation	1143	59.8
Nausea and vomiting	130	6.8
Dyspnoea	91	4.8
Dizziness	48	2.5
Chest discomfort	27	1.4
Oedema	23	1.2
Hypotension	22	1.2
General weakness	19	1.9
Heating sensation	1910	100.0

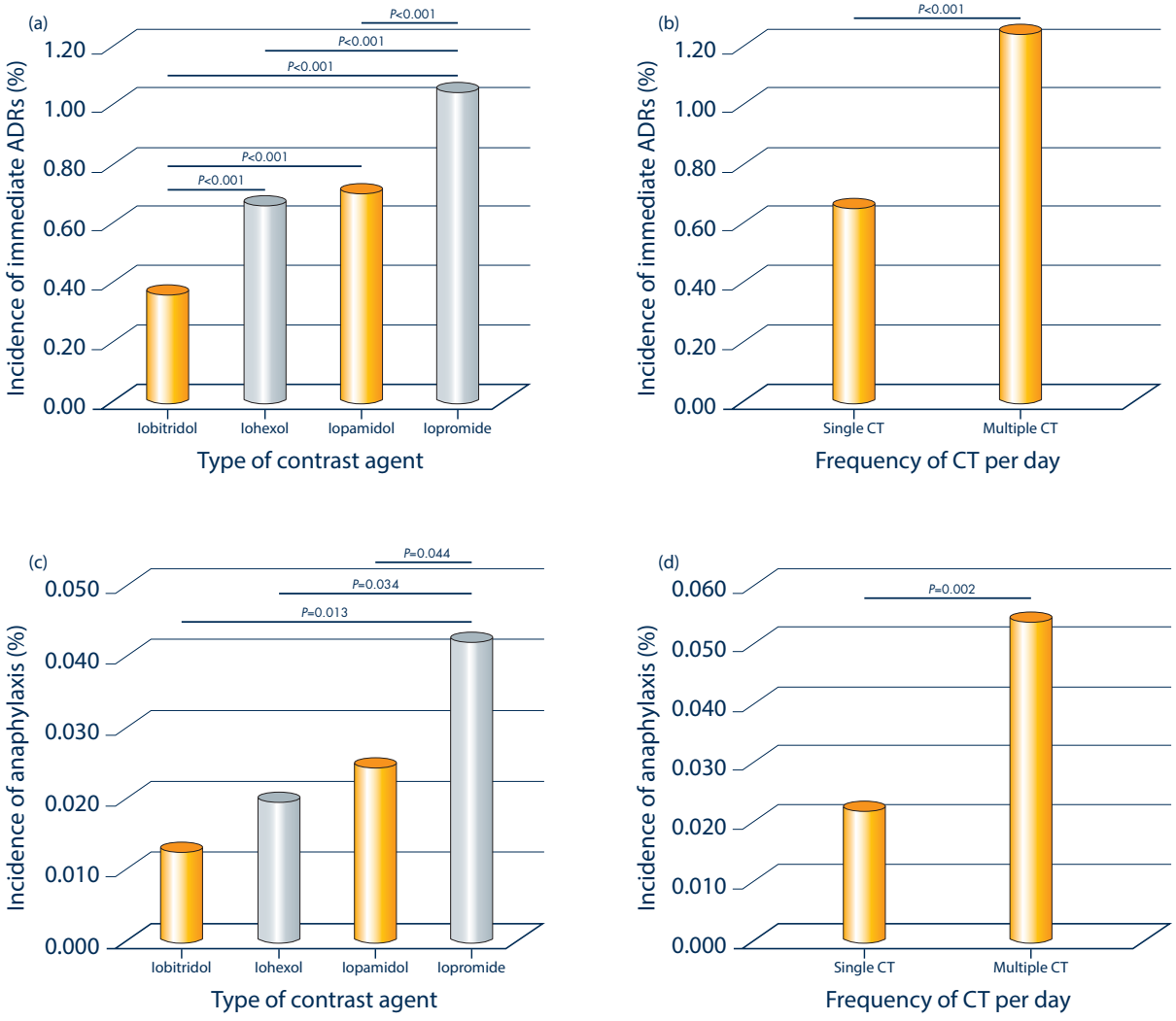
There were 1969 cases of immediate ADR (0.69%) among 286 087 cases in 142 099 patients who underwent contrasted CT examinations. The most frequent cases involved iopamidol (135 882), followed by iohexol (65 764), iopromide (51 685), and **XENETIX®** (32 756). There were 255 336 cases of single CT and 30 751 cases of multiple CT. Specific symptoms were reported in 1910 of 1969 immediate ADRs (97%) (Table 14).

On comparison of immediate ADRs, iopromide (1.03%) had the highest incidence of immediate ADRs by a significant margin ($p < 0.001$). Conversely, **XENETIX®** (0.34%) had the lowest incidence of immediate ADRs by a significant margin ($p < 0.001$). Iohexol (0.64%) did not differ from iopamidol (0.67%; $p = 0.227$; Fig. 12a).

Multiple CT (1.19%) showed a significantly higher incidence than single CT (0.63%; $p < 0.001$; Fig. 12b).

The comparison of anaphylaxis cases indicated that iopromide (0.041%) also had the highest incidence of anaphylaxis by a significant margin ($p = 0.013, 0.034, 0.044$). Iopamidol (0.023%), iohexol (0.018%), and **XENETIX®** (0.012%) did not significantly differ from each other ($p = 0.443$; Fig. 12c). Multiple CT (0.052%) also had a significantly higher incidence of anaphylaxis than single CT (0.020%; $p = 0.002$; Fig. 12d).

Figure 12. **Comparison of immediate ADR incidences according to the type of CM (a) and frequency of CT examinations per day (b). Comparison of anaphylaxis incidences according to the type of CM (c) and frequency of CT examinations per day (d). P values were calculated via chi-square analysis.**



As compared with **XENETIX®**, the odds ratio for iopromide was the highest (OR: 2.718, CI: 2.167–3.409, followed by iopamidol (OR 1.592, CI: 1.281–1.978) and iohexol (OR 1.362, CI: 1.081–1.717). The OR for iopromide was significantly higher than for the other three CMs, and all three CMs had significantly higher ORs for immediate ADR than **XENETIX®**. As compared with single CT, the OR for multiple CT (2.129, CI: 1.890–2.397) was significantly higher ($p < 0.001$). The OR for females (OR 1.505, CI: 1.355–1.672) was also significantly higher than for males ($p < 0.001$). When compared with patients < 20 years old, the OR for those 20–50 years old (OR: 1.548, CI: 1.012–2.369) was significantly higher; however, those older than 50 years did not significantly differ from the other two groups.

As compared with **XENETIX®**, the OR for iopromide was the highest (OR: 6.238, CI: 1.322–29.443), followed by iopamidol (OR: 3.115, CI: 0.683–14.200) and iohexol (OR: 1.913, CI: 0.392–9.646). Only iopromide significantly differed from **XENETIX®** ($p = 0.021$). As compared with single CT, the OR of multiple CT (OR: 3.256, CI: 1.810–5.858) was significantly higher ($p < 0.001$). Gender did not have a significant effect on the incidence of anaphylaxis ($P = 0.142$). Age groups did not significantly differ.

Iopromide showed the highest incidence of immediate ADRs (1.03%) and was followed by iopamidol (0.67%), iohexol (0.64%), and **XENETIX®** (0.34%). In cases of anaphylaxis, iopromide also showed the highest incidence (0.041%), followed by iopamidol (0.023%), iohexol (0.018%), and **XENETIX®** (0.012%). Risk of immediate ADR due to multiple CT examinations (1.19%) was significantly higher than the risk due to a single CT examination (0.63%). Risk of anaphylaxis was also higher for multiple CT examinations (0.052%) than for a single CT examination (0.020%).

The incidence rates of immediate ADRs vary according to the type of low-osmolar non-ionic CM. Iopromide was associated with a higher incidence of immediate ADRs than other CMs, and **XENETIX®** was associated with a lower incidence of immediate ADRs. Furthermore, the administration of multiple contrasted CT examinations per day was associated with a higher incidence of immediate ADRs.

Cardiovascular and thrombotic safety

Cardiovascular adverse events such as myocardial infarction, angina pectoris, vagal malaise, or rhythm disorders or hypotension, vertigo, malaise, tachycardia or cardiac arrest occur very rarely (in < 0.01% of patients) with **XENETIX®**[27-29].

The cardiovascular safety of **XENETIX®** was found to be similar to that of iohexol. Rhythm disorders (respectively 21.7% vs. 13.6%), conduction abnormalities (2.2% vs. 2.3%) and repolarization disorders (21.7% vs. 18.2%) occurred with a similar incidence in patients receiving **XENETIX®** (n = 46) or iohexol (n = 44). Most of these adverse events were of mild or moderate severity and only two cases in the **XENETIX®** group were clinically significant. Moderate increases of the PR interval from pre-contrast agent administration and prolongation of the QT or QTc interval were similar in both groups[83].

There is a risk of clinically significant cardiac electrophysiological adverse events during coronary procedures when contrast agents are delivered via intracoronary route[4, 15].

Transient ST elevation, bradycardia, bundle branch block and ventricular fibrillation occurred in a small proportion of **XENETIX®** 350 recipients (2.6% of 926 patients) in a comparative study in patients undergoing cardiac catheterization; however, significantly fewer iopamidol 340 mg I/mL recipients had such reactions (0.7% of 1093 patients). This difference was due to a higher rate of ventricular fibrillation in **XENETIX®** recipients, requiring direct cardioconversion treatment (0.8% vs. 0%, respectively); however, a rate of 0.8% is very low. Moreover, between-group differences for other cardiac events were not significant[77].

In a different study, thromboembolic complications occurred no more frequently with **XENETIX®** 300 than with ioxaglate 320 mg I/mL in patients undergoing renal angioplasty, of whom most received heparin prior to their procedure (5.7% of 87 patients vs. 3.7% of 80 patients; between-group difference not significant)[80]. Ioxaglate is ionic and was therefore expected to cause significantly fewer thromboembolic complications than **XENETIX®**, which is non-ionic[80].

3.4 Safety in special patient populations

The use of **XENETIX®** was evaluated in a broad range of patient populations, including for example patients at high risk for adverse reactions to iodinated contrast agents and coming from a wide age range.

In at-risk populations

It is well established that the risk of severe adverse events increases in the presence of risk factors for reactions to contrast agents[13].

XENETIX® is well tolerated in at-risk patients; in one of the post-marketing surveillance studies, 98.61% (13,873/14,068) of these patients did not experience product-related adverse events. In this study, the incidence of adverse events was higher in at-risk patients than in those with no pre-existing risk factors (1.39% in at-risk patients vs. 0.81% in patients not at-risk), but serious adverse events did not occur more frequently in the at-risk group. When analysed by risk factor type, Figure 13 shows that adverse events occurred more frequently in patients with a previous reaction to contrast agents, or those with existing asthma and/or allergies, or hypotension or hypertension[70].

In another post-marketing surveillance study, significantly more patients with asthma/allergies (21.9% of 1,849 patients) or renal insufficiency (defined as creatinine level > 1.5 mg/dL or 133 µmol/L ; 10.9% of 950 patients) experienced an adverse event in comparison to the overall population[71]. According to the SPC (see Appendix), clinicians must identify at-risk patients and take appropriate precautions.

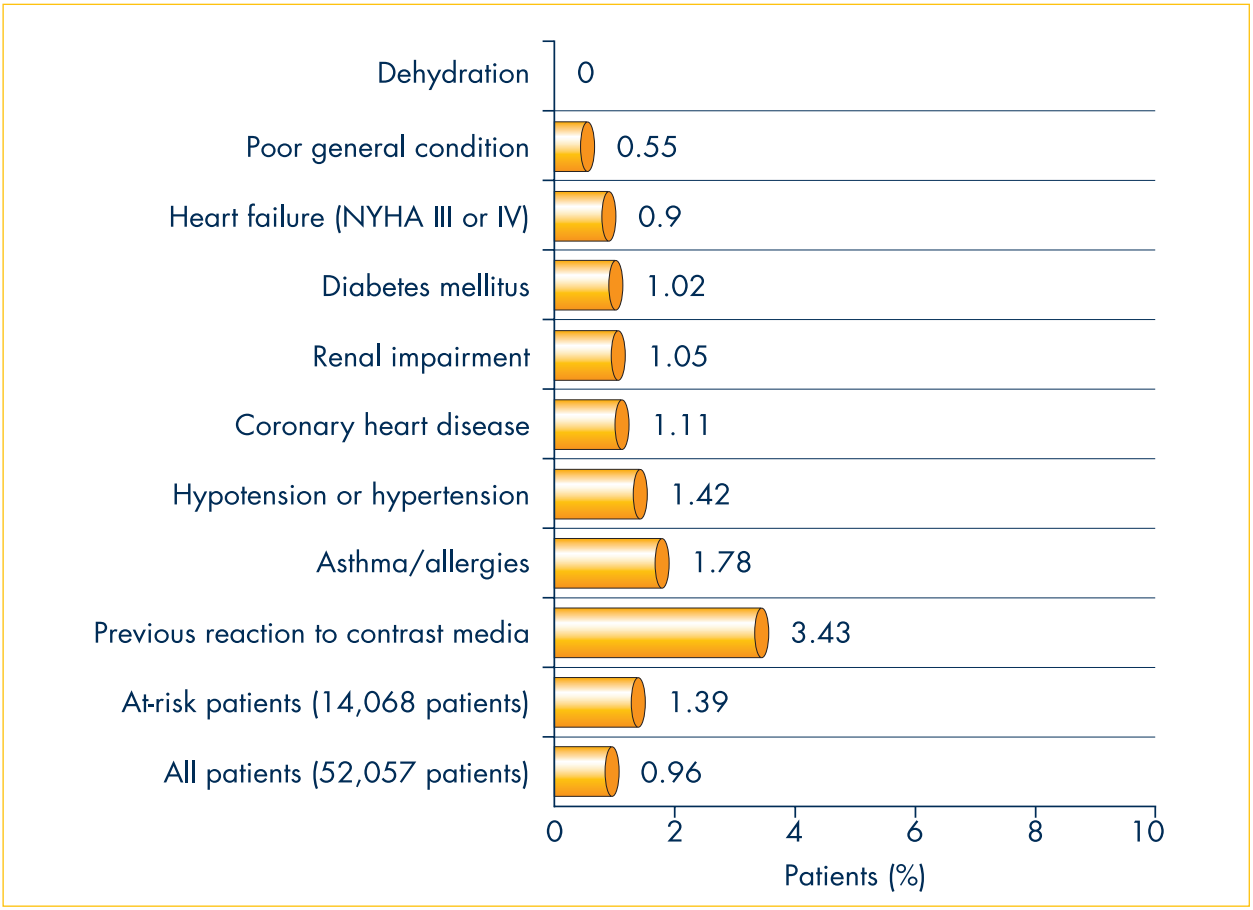


Figure 13. XENETIX® safety in at-risk patients by risk factor in a post-marketing surveillance study. The proportion of patients experiencing adverse events is shown [70]

Paediatric population [70, 93, 94]

XENETIX® is safe to use in paediatric patients. Three out of the 72 patients aged < 15 years in a post-marketing surveillance study of a total patient population of 52,057 experienced adverse events, none of which were serious [70]. **XENETIX®** 300 was as well tolerated as iohexol 300 mg I/mL when given during CT examinations in 80 infants and children aged < 15 years. In this randomised double-blind study, the mean injected volume of contrast agent in either group was 1.8 mL/kg, most patients did not experience an adverse event (Figure 14), and there were no serious adverse events [94]. Heat sensations occurred most frequently in both groups.

In a third study in infants and children aged < 15 years, **XENETIX®** 300 or 350 was as well tolerated or better tolerated than iopamidol 370 mg I/mL when given during angiocardiography. The most common adverse event was vomiting, reported in 5 out of 40 patients in the **XENETIX®** group and 4 out of 40 patients in the iopamidol group, and fever in the iopamidol group (4 out of 40 patients), but these events resolved within 12 hours after the first injection. One death unrelated to contrast agent administration occurred in the iopamidol group. Cardiac effects of **XENETIX®** were also studied. **XENETIX®** was not associated with product-related clinically significant abnormalities in

electrocardiographic parameters, whereas two iopamidol recipients experienced such changes but were not considered complications of contrast agent injections. Increases in heart rate were not different between the groups [93].

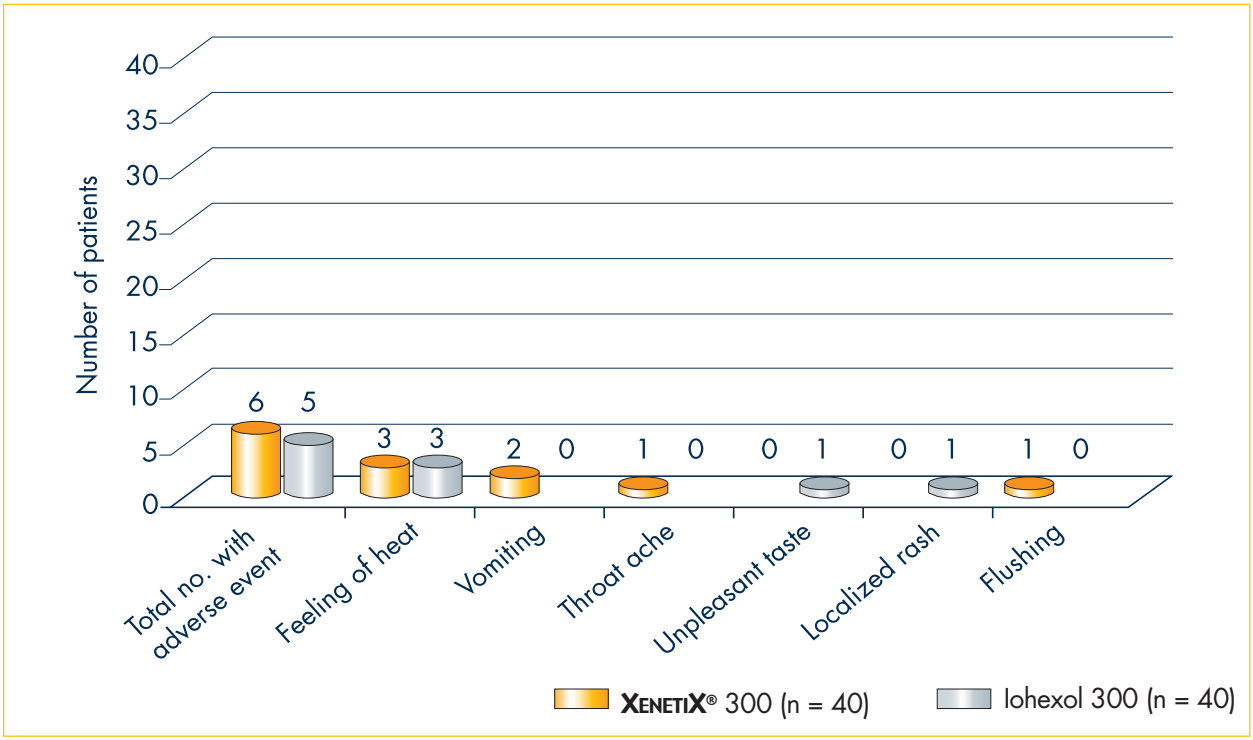


Figure 14. Safety of XENETIX® 300 for CT examinations in paediatric patients. Number of patients experiencing an adverse event [94]

Elderly population

XENETIX® was found to be well tolerated in elderly patients [69, 71]. Patients aged up to 97–101 years were included in post-marketing surveillance studies [69, 71]. When compared with patients aged ≤ 39 years, the incidence of adverse events was lower in patients aged ≥ 60 years [69] or ≥ 70 years [70]; respective rates of adverse events were 0.9% versus 1.7% ($p < 0.001$ [excluding «feeling of warmth»] [69]) in Petersein's study and 0.63% versus 1.40% in Vogl's study [70]. This difference was possibly attributable to a higher immunocompetence in younger patients [69].

Pregnant or breast-feeding women

There are no available **XENETIX®** specific data for pregnant or breast feeding women. The SPC recommends that **XENETIX®** can be used in pregnant and lactating women after careful evaluation of the relative risks and benefits [27-29] based on animal studies (see sections 2.6 and 2.7). The local SPC should be consulted for specific recommendations regarding administration of **XENETIX®** in this patient group.

4. Diagnostic efficacy of XENETIX®

The majority of images obtained with **XENETIX®** 250, 300 and 350 mg I/mL are of good or excellent quality.

Notably, **XENETIX®** 350 was found to be non inferior to iomeprol 400 in terms of diagnostic efficacy and image quality in multi-slice CT angiography (see section 4.4 «CT angiography») despite a lower total concentration of iodine in a prospective, double-blind, randomised study involving 310 patients. Thus, **XENETIX®** offers the potential advantage of better safety due to a lower dose of total iodine injected without compromising efficacy [95].

In comparative clinical trials that recruited patients of a wide age range undergoing various imaging procedures (Tables 14 - 22), the diagnostic efficacy of **XENETIX®** did not differ from that of other non-ionic agents [75, 76, 78, 79, 81-86, 93-95]. Comparative study design details are summarized in Table 15.

Table 15. XENETIX® (iobitridol) comparative study design details [75, 76, 78, 79, 81–86, 93–95]

Randomised and double-blind or open-label design	
Comparators were other non-ionic monomers (e.g. iohexol, iopromide, iopamidol, iomeprol)	
Adults or children (<15 years of age) were enrolled	
Patients usually excluded were pregnant or lactating women and those at high-risk of experiencing contrast reactions such as patients with:	
• Renal impairment • Dehydration • Iodine intolerance or contrast media allergy • Intake of metformin/biguanides within previous 24 hours	• Iodinated contrast agent administration within previous 48 hours • Previous contrast reaction and/or allergies/asthma • Myeloma or pheochromocytoma

Efficacy was generally assessed on image quality, defined as the level of opacification achieved on a 5-point scale: null or unacceptable, poor, fair, good and excellent; two studies used a 4-point scale [84, 95]. A higher score indicates better opacification and thus higher image quality. Efficacy was also assessed on diagnostic quality, defined as whether the examination provided the desired information or diagnosis was obtained (yes/no).
Iodinated contrast agents were delivered intravenously during most examinations except for patients undergoing lower limb angiography [78] or intra-arterial DSA [78], where the intra-arterial route was used, and those having coronary angiography and ventriculography [83].

XENETIX® has demonstrated a good efficacy in adults and children in a wide range of examinations, including its main indications: CT, IV urography, conventional angiography, and CT angiography.

4.1 Computed tomography: XENETIX® 300 or 350

XENETIX® provided similar image quality and diagnostic quality to iohexol and iopromide in CT procedures (Table 16). The most commonly used concentration was XENETIX® 300 and the volume of XENETIX® administered was not different from that of iohexol [82, 84, 86] or iopromide [79]. The efficacy of XENETIX® was demonstrated at a concentration of 350 mg I/mL [82] and 300 mg I/mL [86] in two studies in patients having a cranial CT. Similarly, XENETIX® 300 gave good or excellent image quality in the majority of patients and was therefore similar to iopromide 300 mg I/mL when used for contrast enhancement in abdominal (whole body) CT [79].

When used during dual-phase helical-CT for hepatic and vascular enhancement, XENETIX® 300 and iohexol 300 mg I/mL provided similar hepatic, aorta and portal vein enhancement (Table 17) [84].

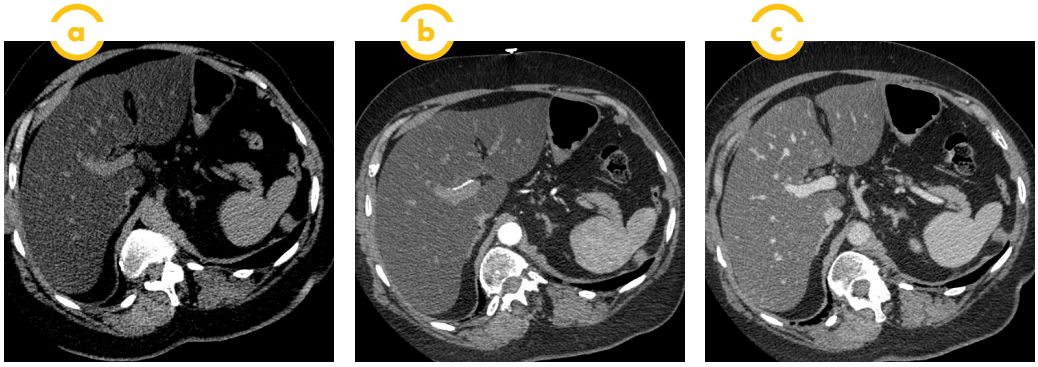
Table 16. XENETIX® efficacy in adults in computed tomography [79, 82, 84, 86]

Reference	Procedure	CM	No. of pts	Strength (mg I/mL) [mean ± SD volume (mL)]	Image Quality (% rated good/ excellent)[a]	Diagnosis Obtained (% «yes»)	AEs (% pts)
Computed tomography (CT) in adults							
Drouillard et al. [82]	Cranial CT	XENETIX®	136	350 [66.1 ± 1.0]	71	98.5	11.0
		iohexol	140	350 [63.9 ± 1.1]	69	97.1	7.2
Taylor and Moseley [86]	Cranial CT	XENETIX®	40	300 [100]	97.5	85	37.5
		iohexol	40	300 [100]	100	90	32.5
Legmann et al. [84]	Hepatic CT	XENETIX®	71	300 [120][b]	97	100	NR
		iohexol	76	300 [120][b]	94	100	NR
Hoogewoud and Woessmer [79]	Whole body CT	XENETIX®	30	300 [130.9 ± 4.6]	83.3	100	30.0
		iopromide	30	300 [132.3 ± 4.5]	86.6	100	36.7

NR = not reported; SD = standard deviation

[a]All studies used a 5-point scale except for Legmann et al., where a 4-point scale was used. Increasing scores up to a score of 4 or 5 indicate better opacification.
[b]Volume reported in methods section of reference; mean volume used not reported.

An example of CT tumoral lesion assessment in steatosic liver pre and post injection at arterial and portal phases, using XENETIX® is shown in Figure 15.



Pre-injection | Post-injection (arterial phase) | Post-injection (portal phase)

Figure 15.

Table 17. **Dual-phase helical CT enhancement of the liver and hepatic aorta and portal veins with XENETIX® (iobitridol) and iohexol[a] [84]**

Mean enhancement, HU ± SD	XENETIX® 300 [300 mg I/mL]	Iohexol [300 mg I/mL]	Statistical Analysis
Liver enhancement			
Arterial phase	13.9 ± 8.87	13.3 ± 9.2	NS
Portal-venous phase	49.94 ± 14.23	48.7 ± 15.88	NS
Aorta enhancement			
Arterial phase	175.94 ± 40.62	175.93 ± 57.33	NS
Portal-venous phase	114.72 ± 29.38	118.00 ± 36.29	NS
Portal vein enhancement			
Arterial phase	50.00 ± 32.87	48.44 ± 31.71	NS
Portal-venous phase	108.85 ± 38.18	112.48 ± 42.53	NS

(Data presented as mean ± SD attenuation in Hounsfield units (HU)), NS = Not Significant

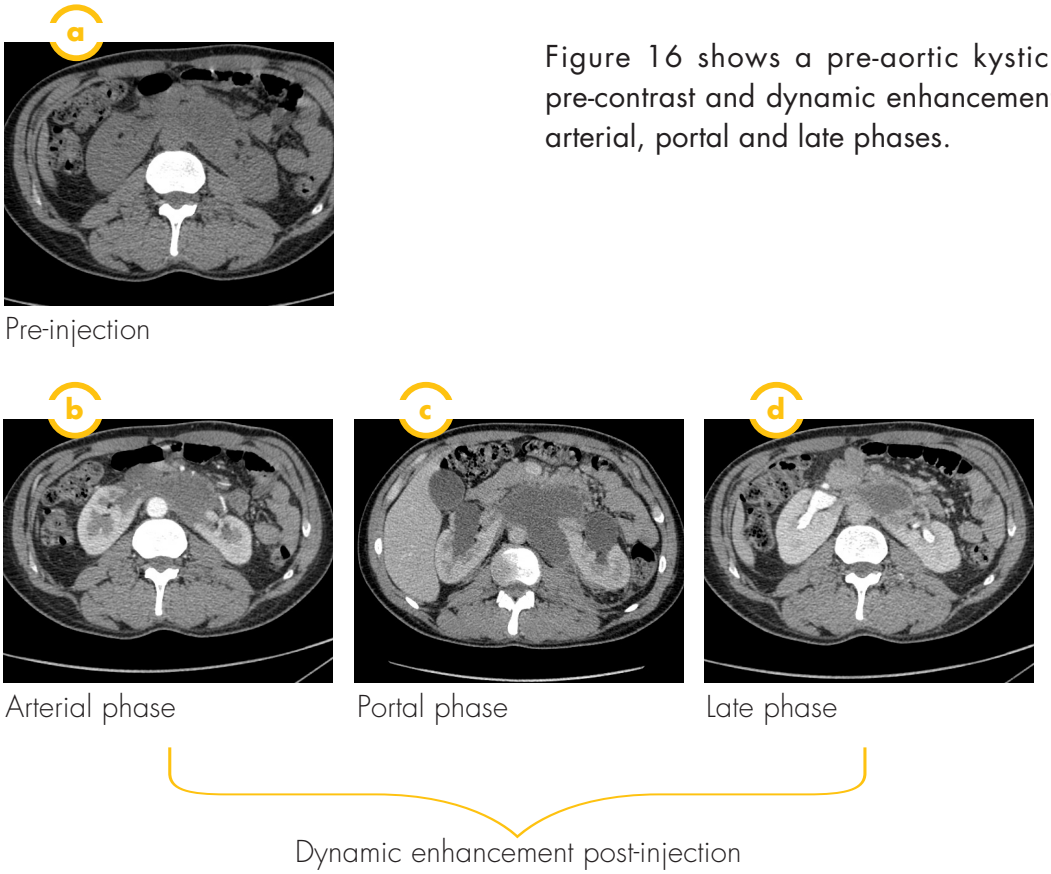


Figure 16 shows a pre-aortic kystic mass, pre-contrast and dynamic enhancement at the arterial, portal and late phases.

Figure 16.

4.2 Intravenous urography: XENETIX® 300 or 350

IV urography is a classical diagnostic method for obtaining both anatomical and functional assessment of the urinary tract [96]. In many institutions, it is nowadays used less frequently than CT urography when urinary tract imaging is required [8].

Image quality was as good with **XENETIX®** 300 as with iohexol 300 mg I/mL. It was rated as good or excellent in 85% and 82% of patients respectively (Table 18) [85]. At higher concentration, **XENETIX®** 350 image quality was assessed as good or excellent as iopamidol 370 mg I/mL and iohexol 350 mg I/mL [75].

Table 18. XENETIX® efficacy in adults in intravenous urography [75, 85]

Reference	Procedure	CM	No. of pts	Strength (mg I/mL) [mean ± SD volume (mL)]	Image Quality (% rated good/ excellent)[a]	Diagnosis Obtained (% «yes»)	AEs (% pts)
Intravenous (IV) Urography in adults							
Meiss et al. [85]	IV Urography	XENETIX® iohexol	87 89	300 [75.7 ± 2.3] 300 [76.2 ± 2.4]	85 82	96.6 97.8	28.7 25.8
Fournier et al. [75]	IV Urography	XENETIX® iopamidol	30 29	350 370	72.0 58.6	86.7 100	26.7 37.9
		XENETIX® iohexol	30 30	350 350	73.3 93.4	100 100	16.7 13.3

SD = standard deviation

[a]All studies used a 5-point scale. Increasing scores up to a score of 5 indicate better opacification.

4.3 Conventional angiography: XENETIX® 250–350

The image quality and diagnostic efficacy of **XENETIX®** was similar to that of iohexol [78, 81, 83], iopamidol [76, 78] and iopromide [76] in a range of conventional angiographic imaging procedures (Table 19).

Table 19. XENETIX® comparative efficacy and safety in adults in angiographic examinations [76, 78, 81, 83]

Reference	Procedure	CM	No. of pts	Strength (mg I/mL) [mean ± SD volume (mL)]	Image Quality (% rated good/ excellent)[a]	Diagnosis Obtained (% «yes»)	AEs (% pts)
Angiography in adults							
Stockx et al. [76]	Lower limb angiography	XENETIX®	30	300	100	100	10.0
		iopromide	30	300	100	100	13.0
		XENETIX®	38	300	86.8	100	76.3
		iopamidol	40	300	90	100	62.5
Lefevre et al. [83]	Coronary & ventricular angiography	XENETIX®	46	350 [133.6 ± 5.6]	100	100	8.8
		iohexol	44	300 [120.7 ± 5.0]	100	100	4.6
Bouard et al. [78]	IV DSA	XENETIX®	39	300	79.5	94.9	
		iopamidol	40	300	90	97.5	
	IA DSA	XENETIX®	30	250	83.3/83.3[b]	100	
		iohexol	30	240	93.3/86.7[b]	100	
Chagnaud et al. [81]	Phlebography	XENETIX®	35	250 [80][c]	80	NR	45.7
		iohexol	38	240 [80][c]	85.7	NR	34.2

DSA = digital subtraction angiography; IA= intra-arterial; IV= intravenous; NR = not reported; SD = standard deviation

[a] All studies used a 5-point scale. Increasing scores up to a score of 5 indicate better opacification.
[b] Opacification quality rated by two observers.
[c] Volume reported in methods section of reference; mean volume used not reported.

In the lower limb examinations, **XENETIX®** 300 and iopromide 300 mg I/mL or iopamidol 300 mg I/mL were given intra-arterially, with no between-group differences in volume administered. Most examinations were required for diagnosis of atherosclerotic disease [76].

The highest dose of **XENETIX®** is used in coronary and ventricular angiography. Visualization of the coronary compartment and any abnormality was considered to be good on images from **XENETIX®** 350 recipients undergoing angiographic examinations of the coronary arteries and heart ventricle. All of the images obtained with **XENETIX®** were rated as having good or excellent quality and allowed a satisfactory diagnosis to be made by the clinician. The efficacy of **XENETIX®** was not significantly different from that of iohexol 300 mg I/mL (reference compound) and similar mean total volumes were used in both groups [83].

In a different study, good or excellent opacification of images was obtained in most patients with suspicion of thrombophlebitis in the lower limbs who received **XENETIX®** during phlebography (venography) [81]. Broadly similar good results were obtained when image quality of the inferior vena cava only was considered. In this study, when administered at a volume of 80 mL, **XENETIX®** 250 had similar efficacy to that of iohexol 240 mg I/mL [81]. However, digital substraction angiography (DSA), magnetic resonance angiography and multi-detector CT (MDCT) angiography are more commonly used today in the evaluation of lower extremity arterial disease [97].

4.4 CT angiography: XENETIX® 350

Images in all territories

Conventional coronary examinations are invasive whereas CT angiography is non-invasive and can identify coronary calcifications easily, allowing accurate measurements of lesion length in a way that conventional angiography cannot [98]. Using **XENETIX®** 350 in CT angiography provide excellent images in all territories, from head to foot.

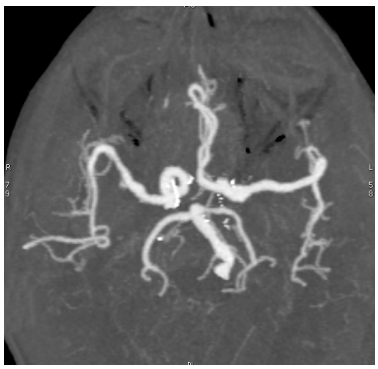


Figure 17.

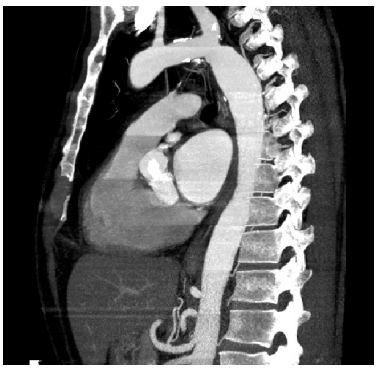


Figure 18.

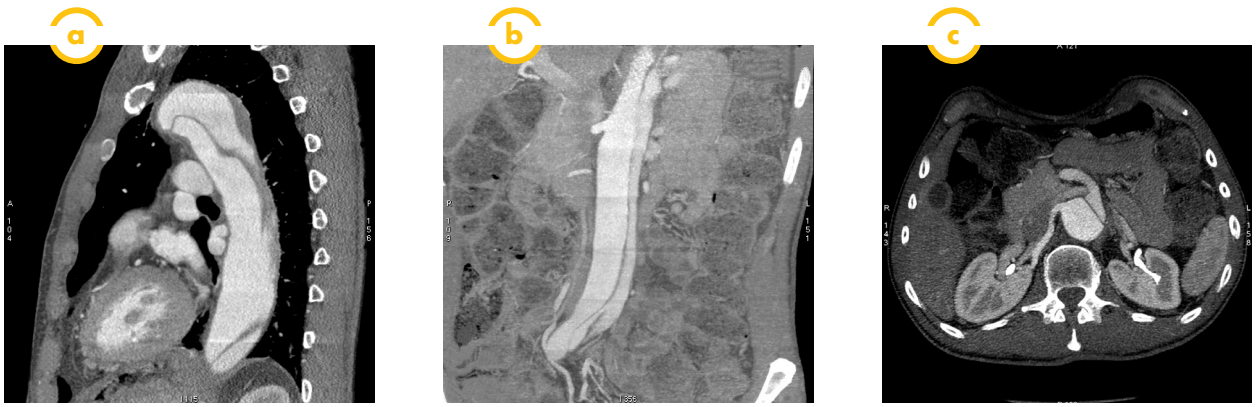


Figure 19.

The figure 17 provides a circle of willis imaging showing a sylvian aneurism, then moving to the thorax, the figure 18 shows an aortic coarctation. Going down to the abdomen, the figure 19 provides a reconstruction in different axis of a thoraco-abdominal aortic dissection. At the level of the lower limb, the figure 20 shows an embolic occlusion of the left poplital artery. Gilard et al. concluded that MDCT methodology may offer a non-invasive alternative to conventional coronary angioplasty [99]. Figure 21 provides an example of coronary angiogram derived after a volumetric 3-dimensional CT cardiac angiography examination.

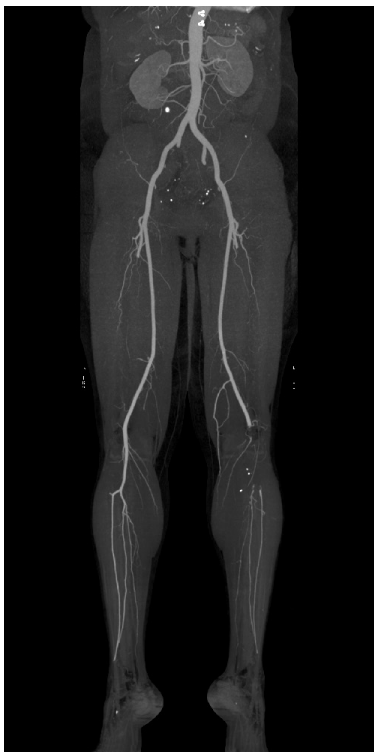


Figure 20.

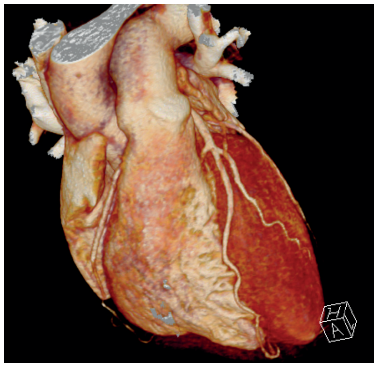


Figure 21. Coronary CT angiography

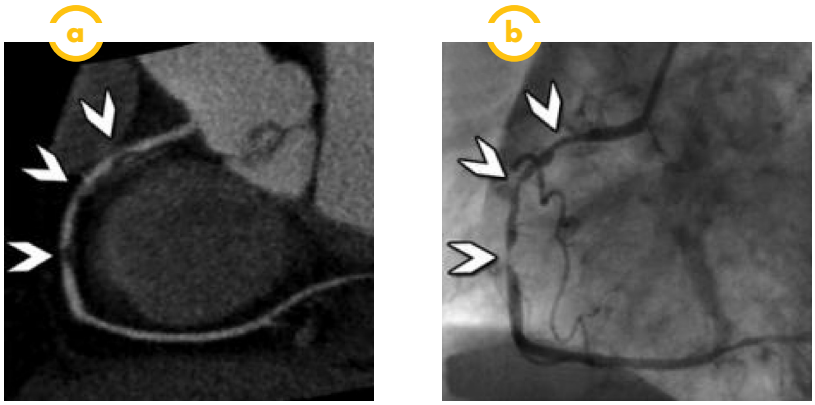


Figure 22. Stenoses in the right coronary artery in a 59 – year – old woman [Image A shows 3 significant stenosis (arrowheads) on a curved maximum intensity projection («CATH view») obtained by CT, and image B shows the stenoses on the conventional angiogram [100]]

XENETIX® 350, (80 mL, dual phase injection with saline flush of 40 mL) was used successfully in a 320-slice CT coronary angiography study in 30 patients with suspected coronary artery disease. Combining cardiac CT, an emerging technology, with the use of **XENETIX®** 350 makes it possible to significantly reduce the radiation dose and amount of contrast agent required compared with conventional coronary angiography (CCA) while maintaining high diagnostic accuracy [100] (Figure 22).

Various factors influence image quality, e.g. patient-related factors (body weight, cardiac output), injection parameters (volume and injection rate), contrast agent parameters (iodine concentration), and factors relating to the type of procedure itself such as acquisition timing [101]. Two studies investigated the influence of contrast agent parameters on the comparative efficacy of **XENETIX®** 350 [95, 102].

The study by Loewe et al. compared the efficacy of **XENETIX®** 350 with that of iomeprol 400 mg I/mL in patients undergoing MDCT of the abdominal aorta and/or the abdominal arteries [95].

Table 20. XENETIX® comparative efficacy and safety in adults in angiographic examinations [95]

Reference	Procedure	CM	No. of pts	Strength (mg I/mL) [mean ± SD volume (mL)]	Image Quality (% rated good/ excellent)[a]	Diagnosis Obtained (% «yes»)	AEs (% pts)
Angiography in adults							
Loewe et al. [94]	Abdominal aorta and arterial CT angiography	XENETIX®	153	350 [101.0]	94.7	99.3	1.3
		iomeprol	154	400 [101.5]	94.8	99.4	0.65

[a] Study used a 5-point scale. Increasing scores up to a score of 5 indicate better opacification.

There was no significant between-group difference for image quality and vascular wall visualization (Table 20). Moreover, the diagnostic efficacy of **XENETIX®** 350 was non-inferior to that of iomeprol 400 mg I/mL, thus offering the safety advantage of a lower iodine dose without compromising efficacy (Figure 22). The mean total dose of iodine after **XENETIX®** 350 administration was 35.4 g (range 24.5–49.0) and 40.6 g (range 25.2–56.0) after iomeprol 400 mg I/mL administration, yet the efficacy of **XENETIX®** was non-inferior to that of iomeprol confirming that a lower total amount of iodine does not yield inferior diagnostic contribution results. Moreover, the lower iodine concentration after **XENETIX®** administration in no way adversely affected the relative variation from baseline in arterial enhancement (expressed in Hounsfield Units [HU]). The mean signal intensity relative variations from baseline were 8.123 (± 5.9) in the **XENETIX®** group (n = 1,160 vascular ROIs) and 8.863 (±5.5) in the iomeprol group (n = 1,152 vascular ROIs), with no significant between group difference (mean pre- and post-contrast arterial opacification values were 40.0±12.1 HU and 320.4±93.5 HU with **XENETIX®** and 40.8±12.5 HU and 353.6±95.5 HU with iomeprol) [95] (Table 21).

Notably, there was no study-predefined injection protocol for injection rate and volume (although maximum volume limit was set at 150 mL) [95].

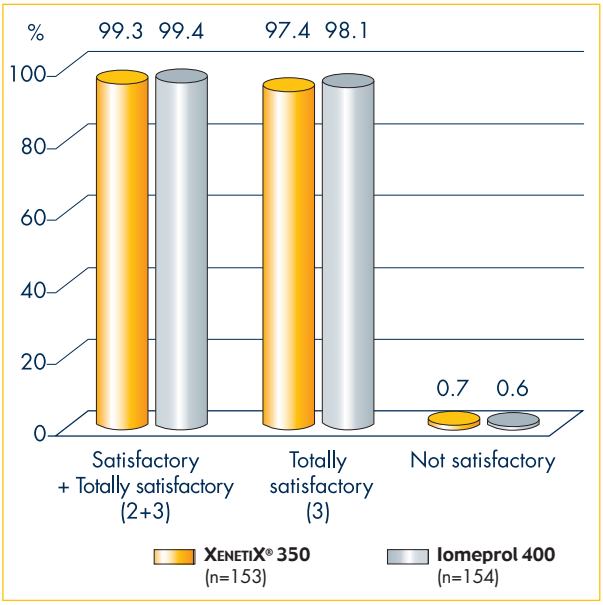


Figure 23. Diagnostic efficacy of XENETIX® 350 for CT angiography of the abdominal aorta and abdominal arteries [95]

Table 21. XENETIX® 350 efficacy in CT angiography of the abdominal aorta and abdominal arteries [95]

	XENETIX® 350 mg I/mL	Iomeprol 400 mg I/mL	Statistical Comparison
Diagnostic efficacy[a] [% pts with image rated as «satisfactory» or «totally satisfactory»]	99.3 [n = 153]	99.4 [n = 154]	p = 0.00002 95% CI [–2.98%; 3.01%]
Image quality [% vessel segments with rating of «good» or «excellent» for image quality]	94.7 [2,319/2,448 segments]	94.8 [2,336/2,464 segments]	p = 0.30
Vascular wall visualization [% vascular segments with rating of «good» or «excellent» for image quality]	84.3 [2,064/2,448 segments]	83.2 [2,049/2,464 segments]	p = 0.83
Attenuation relative variations from baseline[b]	8.123 [1,160 vascular ROIs]	8.863 [1,152 vascular ROIs]	p = 0.0673

[a]Primary endpoint; non-inferiority confirmed because 95% CI excludes α value of -10%. P-value is exact value for main effect (which is that the difference between the products is not equal to 10%).
[b]Due to higher iodine concentrations, absolute signal intensity (HU) higher with iomeprol 400 (p = 0.0014)

n = number of patients - CI = confidence interval

Some participating study centres used a fixed volume and injection rate, regardless of patient characteristics (e.g. bodyweight); subjects in these centers comprised 48% of patients overall. Other centers determined these parameters on a patient-per-patient basis. Consequently, the influence of different iodine concentrations on efficacy could be accurately examined, regardless of injection protocol. This study design further strengthens the observations that **XENETIX®** 350 can provide the same opacification, image quality and diagnostic efficacy at a lower iodine dose than iomeprol. The authors also concluded that iodine concentration and iodine flux influence diagnostic and image quality to a lesser degree than previously thought, particularly when ultra-fast MDCT (using 64-slice or dual-source) scanners are used in such angiographic examinations [95].

In a different study, aortic opacification was longer with **XENETIX®** 350 than with ioxithalamate 350 mg I/mL (an ionic HOCM) in CT angiography examinations, suggesting that differences in physicochemical properties of iodinated contrast agents may possibly have some influence on imaging efficacy; however, there was no significant difference in the decrease of aortic opacification under a 200 HU threshold between **XENETIX®** 300 and ioxithalamate 350 mg I/mL. [102].

In conclusion, LOCM like **XENETIX®** can be recommended in angiographic CT examinations where long acquisition times are needed.

A recent study[103] compared **XENETIX®** 350 to two CM with higher iodine concentrations for coronary CTA: iopromide 370 mg/ml (Ultravist®) and iomeprol 400 mg/ml (Iomeron®). The main objective of the study was to demonstrate the statistical non-inferiority of **XENETIX®** 350 compared to the best of the two comparators in terms of image quality and interpretability as measured by the rate of patients with CTscans evaluable for the identification of coronary artery stenosis.

This study was a non-inferiority, multicentre, randomized, double-blind, clinical trial on three parallel groups. Patients were included in 23 centres from five countries between November 2010 and September 2012 and randomized on a 1:1:1 ratio to undergo clinically indicated coronary CTA after injection of iobitridol (**XENETIX®**), iopromide or iomeprol.

Symptomatic adult patients with suspected coronary artery disease (CAD), and scheduled for coronary CT angiography were enrolled in this study. Patients could not be included if they had both a contraindication to -blocker medications and a baseline heart rate above 65 beats per minute (bpm). Additional reasons for exclusion were the presence of arrhythmias or non-sinus rhythm, coronary artery bypass grafts or stents, artificial heart valves, moderate to severe aortic valve stenosis, hyperthyroidism, clinical instability, severe renal failure or previous injection of any CM within 48 hours prior to the study.

For each patient, one of three CM was delivered intravenously. Delivered volume and delivery rate of CM was consistent for the three CM but varied according to patient body weight (BW): 60 mL injected at 4 mL/s for a BW<60 kg, 75 mL at 5 mL/s for a BW between 60 and 80 kg, 90 mL at 6 mL/s for a BW>80 kg. Therefore, the iodine-delivery rate was lowest for **XENETIX®**. CM was warmed and injections were followed by a 100 % saline flush of 75 mL administered at the same rate as the CM.

A total of 468 patients were included (58 % male; aged 57.8 ± 12.4 years). Therefore, 452 patients were analysed in the FAS and 463 in the safety set. There were no significant differences between the three groups in terms of demographics, clinical symptoms, risk factors and pre-CTA heart rate. No differences were noted in terms of requirement for βblockers for the CTA procedure, calcium score and radiation dose.

The rate of patients with evaluable CT scans was not significantly different between the three groups (92.1 %, 95.4 % and 94.6 % of patients in the FAS, for **XENETIX®**, iopromide and iomeprol, respectively) (Figure 24). The 95 % CI of the difference between **XENETIX®** and the best of the two comparators (iopromide) was [-8.8 to 2.1], demonstrating the non-inferiority of iobitridol, when compared to other CMs, in its ability to allow CAD diagnosis through a complete assessment of coronary artery segments. The average score for image quality per-segment (total number of segments = 6,220) was 3.5 ± 0.9, 3.5 ± 0.8 and 3.4 ± 0.9 for the **XENETIX®**, iopromide and iomeprol groups, respectively (p>0.05).

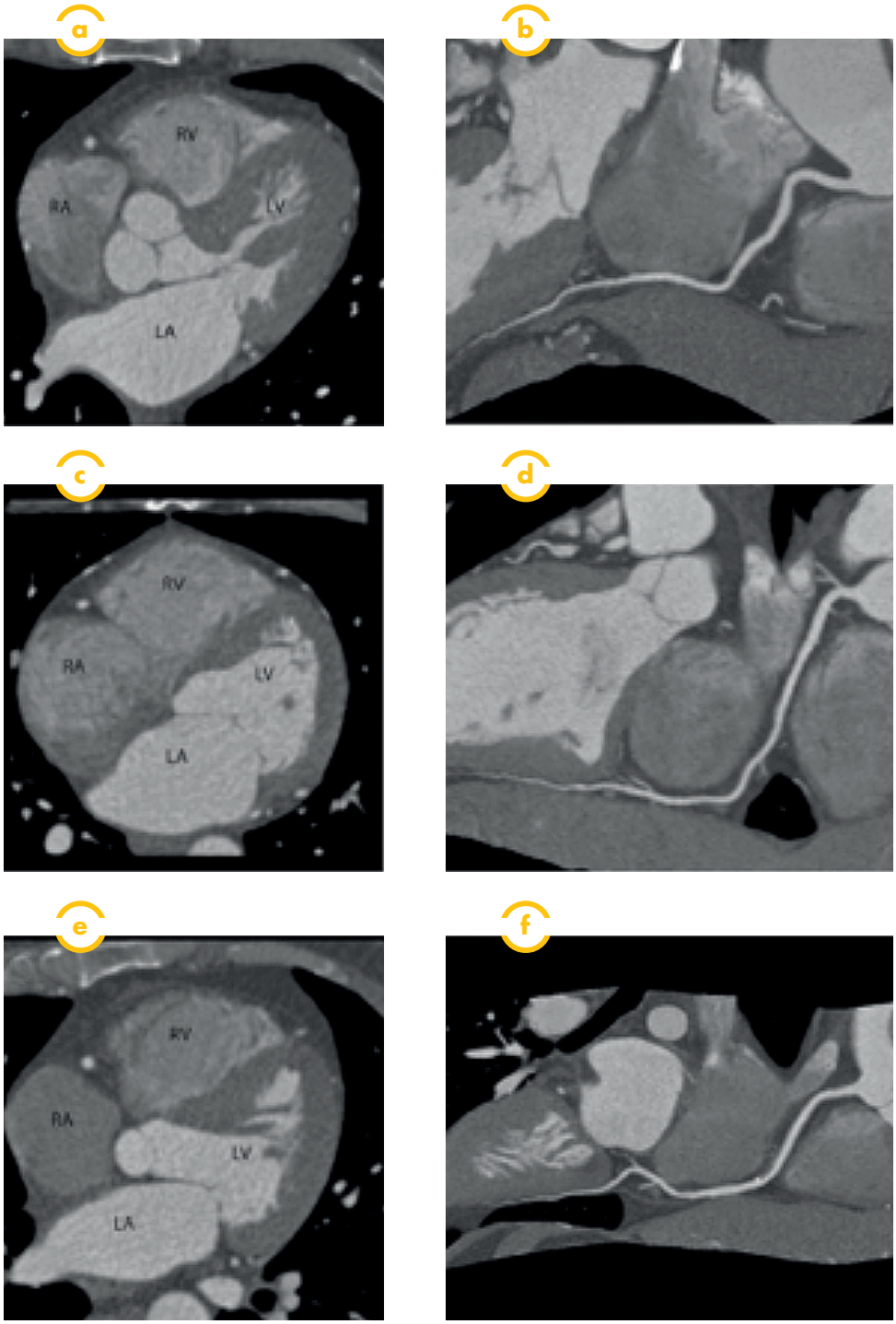


Figure 24. Transaxial cross-sections (0.6-mm slice width) and curved multiplanar reconstructions of the right coronary artery, all displayed at a window level of 1,200 and width of 200 HU. (a, b) Investigation performed using iobitridol 350 mg/ml. (c, d) Investigation performed using iopromide 370 mg/ml. (e, f) Investigation performed using iomeprol 400 mg/ml. LA left atrium, LV left ventricle, RA right atrium, RV = right ventricle.

The average pre-contrast vascular attenuation calculated from values of the ascending aorta, LM and left ventricle was 42.2 ± 9.7 HU, without any difference between the three groups (p = 0.993). Vascular attenuation was significantly increased in post-contrast images as compared to pre-contrast images in all three structures. Average post-contrast arterial vascular attenuation was 426.3 ± 92.9 HU, 449.8 ± 88.1 HU and 466.4 ± 104.6 HU for the **XENETIX®**, iopromide and iomeprol groups, respectively (p = 0.001).The difference between groups was statistically significant for absolute values; however, when values accounting for noise were plotted as SNR and CNR, differences were no longer significant. Measurements of noise in the ascending aorta showed no significant difference between groups (p = 0.311).

No difference was observed regarding the number of significant stenoses identified with the three CMs (p=0.580). The mean score for comfort of the examination rated by the patient was good (4.4± 0.6) and similar for all three groups. Patient comfort was confirmed by a low reported intensity of pain (mean score of less than 1 out of 10 cm on VAS for the three groups). Regarding patient management, no action was required after the CTA for 73 % of the patients overall, with no significant difference between groups.

The percentage of patients experiencing post CM-injection AEs was 15.1%; 19.5%and 15.1%, for the **XENETIX®**, iopromide and iomeprol groups, respectively. Most AEs concerned cardiac disorders, which were reported through systematic ECG follow-up performed up to 10 min post-injection. Overall, mean heart rate was similar in all three groups.

One severe AE was reported in the iomeprol group (one severe injection site pain assessed as possibly related to contrast agent). Only mild events were reported with **XENETIX®** while four and seven moderate events were reported with iopromide and iomeprol, respectively. Few post-CMAEs were considered possibly related to CM administration: two in the iobitridol group and five in the iopromide group as well as in the iomeprol group. The cardiac events considered possibly related to CM injection were bradycardia (one patient in each group) and extrasystoles (two patients in the iomeprol group). Other possibly related events were pain in the iobitridol group, injection site pain, nausea, headache and urticaria in the iopromide group, injection site pain and feeling hot in the iomeprol group.

With current CT technology, **XENETIX®** 350 mg is not inferior to CMs with higher iodine in terms of image quality for coronary stenosis assessment by CTA. When considering image quality, SNR and CNR, **XENETIX®** yielded similar values to iopromide and iomeprol. **XENETIX®**, with a lower content of iodine, holds the potential to reduce the risk of adverse reactions, as supported by its excellent safety profile (see chapter 3: Clinical Safety of **XENETIX®**).

4.5 Paediatric indications: XENETIX® 300 or 350

XENETIX® 300 showed similar efficacy to iohexol 300 mgI/mL in paediatric cranial or abdominal contrast-enhanced CT (Table 22). Approximately just over one-half of the children enrolled were examined for suspicion or follow-up of a tumour, the remainder had neurologic symptoms, infectious or systemic disease, hormonal disorders or trauma. The agents were administered rapidly, with duration of injection being between 30 seconds and 1 minute. The mean volume injected per kilogram body weight was 1.8 mL/kg in both groups [94].

Table 22. XENETIX® efficacy in children in computed tomography [93]

Reference	Procedure	CM	No. of pts	Strength (mg I/mL) [mean ± SD volume (mL)]	Image Quality (% rated good/ excellent)[a]	Diagnosis Obtained (% «yes»)	AEs (% pts)
Computed tomography (CT) in children							
Smets and Shaw [93]	Cranial or body CT	XENETIX®	40	300 [≤100]	100	100	15
		iohexol	40	300 [≤100]	100	100	12.5
SD = standard deviation							
[a]Study used a 5-point scale. Increasing scores up to a score of 5 indicate better opacification.							

XENETIX® 350 also provided good contrast efficacy in paediatric angiocardiography, similar to that achieved with iopamidol 370 mg I/mL [93] (Table 23). In this study, most patients required angiocardiography for better anatomic definition of their congenital heart disease. Notably, 85% of patients in this study had repeat injections and thus exceeded the protocol-defined maximum total dose of 2 mL/kg bodyweight (in children) or 8 mL/kg (in neonates). This was attributed to higher doses used in participating centres (e.g. differences in centre practice and whether the unit was equipped with a biplane imager) [93]. Cardiac catheterization is necessary as a diagnostic procedure in paediatric patients when non-invasive methods cannot offer a complete anatomical diagnosis or when clinical signs and symptoms are not consistent with the diagnosis or when the patient's clinical course deviates from expectations [104].

Table 23. XENETIX® comparative efficacy and safety in children in angiocardiographic examinations [92]

Reference	Procedure	CM	No. of pts	Strength (mg I/mL) [mean ± SD volume (mL)][a]	Image Quality (% rated good/ excellent)[b]	Diagnosis Obtained (% «yes»)	AEs (% pts)
Angiocardiography in children							
Rossignol et al. [93]	Angiocardiography	XENETIX®	40	350 [2-8][a]	87.5	97.5	15
		iopamidol	40	370 [2-8][a]	82.5	90	30
[a]Dose (mL/kg) reported in paediatric study [79]. [b]Study used a 5-point scale. Increasing scores up to a score of 5 indicate better opacification.							

5. Conclusion

The use of XENETIX® in medical imaging radiographic procedures is now well established.

It is one of the lastest non-ionic monomeric LOCMs available, and the only agent with a unique chemical structure designed for stabilized hydrophilicity, which in theory may offer the safety advantage of being less likely to interact with proteins in cell membranes or plasma.

Safety data in 4 large scale post-marketing surveillance studies (more than 300.000 patients included) and numerous clinical trials show that XENETIX® is well tolerated.

The majority of imaging procedures performed with XENETIX® 250-350 mg I/mL are of good or excellent quality. XENETIX® 350 provided diagnostic efficacy and image quality in multi-slice CT angiography non inferior to that of iomeprol 400 mg I/mL even with a lower average iodine dose for XENETIX® 350.

XENETIX® is available in a range of concentration and volumes, and more importantly, is also available in the unique ScanBag® delivery system thus providing maximum flexibility to the radiologist in selecting the appropriate dose and method of administration on a patient-per-patient basis.

We would like to extend our sincere thanks to Pr. Laissy (Bichat Hospital, Department of Radiology, Paris, France) and Dr. Dewey (Charité, Medical School, Department of Radiology, Berlin, Germany) who kindly provided the images included in this product monograph.

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Appendix
Summary of Product Characteristics

Xenetix® 350, solution for injection (350 mgI/ml) ; **Xenetix® 300**, solution for injection (300 mgI/ml) ; Xenetix® 250, solution for injection (250 mgI/ml) – **Composition per 100 ml: Xenetix® 350:** 76.78 g of iobitridol (corresponding to 35 g of iodine), **Xenetix® 300:** 65.81 g of iobitridol (corresponding to 30 g of iodine), **Xenetix® 250:** 54.84 g of iobitridol (corresponding to 25 g of iodine) – **Indications(**):** this product is for diagnostic use only. **Contrast agent for use in: Xenetix® 350** intravenous urography, computed tomography, intravenous digital substraction angiography, arteriography, angiocardiography – **Xenetix® 300:** intravenous urography, computed tomography, intravenous digital substraction angiography, arteriography, angiocardiography, endoscopic retrograde cholangiopancreatography, arthrography, hysterosalpingography – **Xenetix® 250:** phlebography, computed tomography, intra-arterial digital substraction angiography, endoscopic retrograde cholangiopancreatography – **Posology and method of administration (*):** the doses should be adapted to the examination and the territories intended to be opacified, as well as to the weight and renal function of the subject, particularly in children – **Contraindications (*):** hypersensitivity to iobitridol or any of the excipients, history of major immediate or delayed skin reaction (see undesirable effects) to Xenetix®, manifest thyrotoxicosis, hysterosalpingography during pregnancy. – **General comments for all iodinated contrast agents (*):** in the absence of specific studies, myelography is not an indication for Xenetix®. All iodinated contrast media can cause minor or major reactions that can be life-threatening. They may occur immediately (within 60 minutes) or be delayed (within 7 days) and are often unpredictable. Because of the risk of major reactions, emergency resuscitation equipment should be available for immediate use. – **Precautions for use (*):** intolerance to iodinated contrast agents, renal insufficiency, hepatic insufficiency, asthma, dysthyroidism, cardiovascular diseases, central nervous system disorders, pheochromocytoma, myasthenia: **Interaction with other medicinal products and other forms of interaction (*)** – beta-blocker substances, diuretics, metformin, radiopharmaceuticals, interleukin II – **Fertility, pregnancy and lactation (*) – Undesirable effects (*):** hypersensitivity, anaphylactic reaction, anaphylactoid reaction, anaphylactic shock, angioedema, urticaria, erythema, pruritus, eczema, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, Lyell's syndrome, maculopapulous exanthema, bronchospasm, laryngospasm, laryngeal oedema, dyspnoea, sneezing, cough, tightness in throat, nausea, vomiting, abdominal pain, agitation, headache, vertigo, hearing impaired, presyncope, tremor, paresthesia, somnolence, convulsions, confusion, visual disorders, amnesia, photophobia, transient blindness, coma, feeling hot, facial oedema, malaise, chills, tachycardia, arrhythmia, ventricular fibrillation, hypotension, circulatory collapse, hypertension, angina pectoris, myocardial infarction, cardiac arrest, torsades de pointes, coronary arteriospasm, respiratory arrest, pulmonary edema, thyroid disorder, acute renal failure, anuria, blood creatinine increased, injection site pain, inflammation, oedema, necrosis following extravasation. – **Overdose (*) – Pharmacodynamic properties (*):** Pharmacotherapeutic group: Water-soluble, contrast **medium with low osmolarity; ATC code: V08AB11. Presentation (**): Xenetix 250:** 50 ml, 100 ml, 200 ml or 500 ml glass vials, Xenetix 300/350: 20 ml, 50 ml, 60 ml, 75 ml, 100 ml, 150 ml, 200 ml or 500 ml glass vials and 100 ml, 150 ml, 200 ml or 500 ml polypropylene bags. **Marketing authorisation holder (*):** Guerbet - BP 57400 - F-95943 Roissy CdG cedex – FRANCE. **Information:** tel: 33 (0) 1 45 91 50 00. **Revision:** September 2015.

(*) For complete information please refer to the local Summary of Product Characteristics.
(**) Indications, volumes and presentations may differ from country to country.
Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

Our Mission:

- **Guerbet's men and women are committed to offering health professionals contrast agents, medical devices and innovative solutions indispensable to diagnostic and interventional imaging to improve patients' prognosis and quality of life.**
- **Passionate about our business, we strive day in, day out to combine performance, quality and sustainable development.**

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