Guerbet

Xenetix®

Iobitridol

Clinical safety

proven by real-world evidence

Backed by Guerbet's continuous commitment to the field of contrast media, XENETIX® provides you with a large panel of Real World Evidence (RWE)[1-5] to help advance your real world imaging.

REAL-WORLD EVIDENCE | PETERSEIN J. ET AL, 2003 | VOGL TJ. ET AL, 2006 | WENDT-NORDAHL G. ET AL, 2006 | MAURER M. ET AL, 2011 | GORODETSKI B. ET AL, 2020 | CLINICAL SAFETY OF XENETIX® | ABOUT XENETIX®

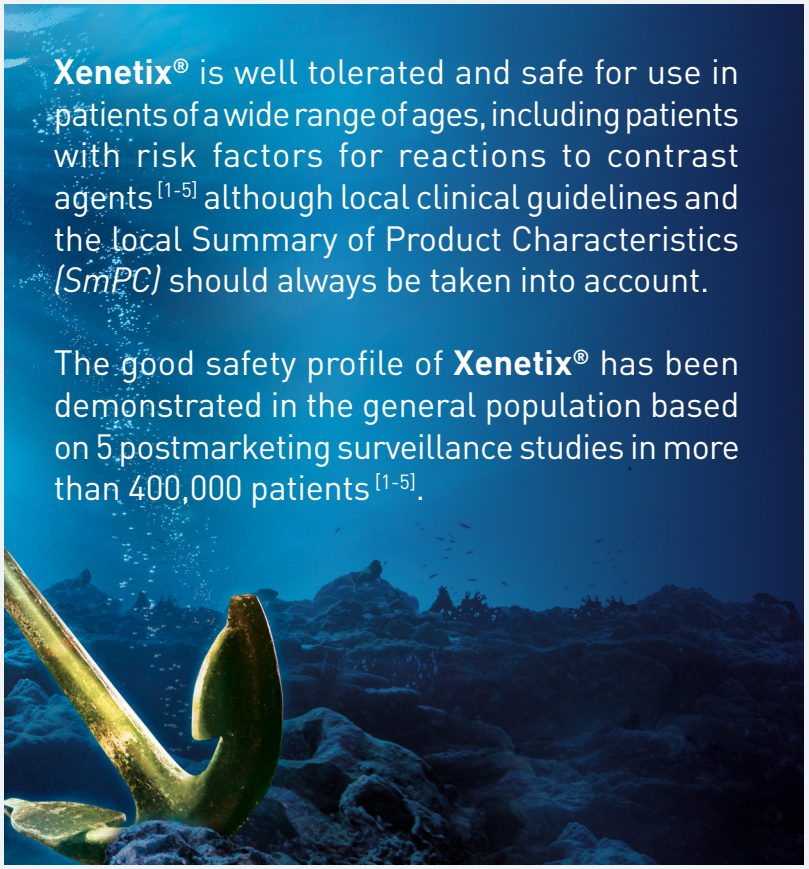
Xenetix® - Clinical Safety **Anchored in RWE**

Iobitridol

Real-World Evidence *(RWE)**

- RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from RWD analysis *(Real World Data)*.
- RWE can be generated by different study designs or analyses, including but not limited to randomized trials, such as large simple trials, pragmatic trials, and observational studies *(prospective and/or retrospective)*.
- RWE complements clinical trials data by providing insights that trials can't. **This combination could guide healthcare professionals' diagnosis and treatment decisions on what works best on specific patient populations.**

*FDA definition



Petersein J. *et al*, Eur Radiol. 2003;13(8):2006-2011

RESULTS OF THE SAFETY AND EFFICACY
of iobitridol in more than 61 000 patients

OBJECTIVE

Assess the safety and the diagnostic efficacy of the **Xenetix®** (iobitridol), a non-ionic contrast agent.

METHODOLOGY

- **Large postmarketing surveillance study** conducted in Germany between 1996 and 2000

- **61,754 patients**

- **Mean age**
57.4 years (0-97)

- **Safety** assessed with standardized questionnaires

- **Data collection**
  - Demographic data
  - Pre-existing risk factors
  - Comedication
  - Premedication
  - Contrast medium injection
  - Assessment of the quality of images
  - Assessment of the diagnostic yield of the examination
  - Adverse events

- **High-risk patients**
28.8%
19.1% of patients had one risk factor

Petersein J. *et al*, Eur Radiol. 2003;13(8):2006-2011

RESULTS OF THE SAFETY AND EFFICACY
of iobitridol in more than 61 000 patients

RESULTS

- Only 2.3% of the patients experienced adverse events (AEs).
- The percentage of AE was higher in the younger population.

Younger patients (15–39 years)	Older patients (60+ years)
1.7%	0.9%

$p<0.001$

- The "feeling of warmth" was observed in 1.1% of all patients.
- The percentage of AEs was independent of the concentration and dosage of iodine used.
- The causal relationship between adverse events and **Xenetix®** was rated as probable in 0.9% of the patients.
- In 89.8% of cases, image quality was rated as "excellent" or "good".

Petersein J. *et al*, Eur Radiol. 2003;13(8):2006-2011

RESULTS OF THE SAFETY AND EFFICACY
of iobitridol in more than 61 000 patients

SAFETY OF IOBITRIDOL IN THE GENERAL POPULATION
and at-risk patients

OBJECTIVE

Review the rate of adverse events after the administration of **Xenetix®** (iobitridol) under daily clinical practice conditions in the general population and in at-risk patients.

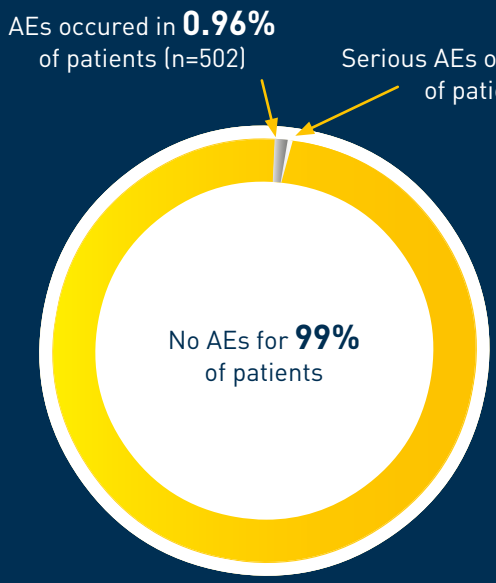
METHODOLOGY

- **Large postmarketing surveillance study** conducted in Germany between 2000 and 2004
- **52,057 patients**
- **Sex**
  Men 48.74%, Women 48.87%, Undertermined gender 2.38%
- **Mean age**
  58.96 years (4-98)
- **Safety** assessed with standardized questionnaires
- **Data collection**
  - Patient data (age, sex, height, weight)
  - Pre-existing risk factors
  - Premedication administered
  - Type of examination
  - Contrast medium injection
  - Adverse events
- **High-risk patients**
  27.02%
  - Renal impairment
  - Heart failure
  - Hypotension or hypertension
  - Coronary artery disease
  - Previous reaction to contrast media
  - Asthma and/or allergies
  - Dehydration
  - Diabetes mellitus
  - Poor general condition

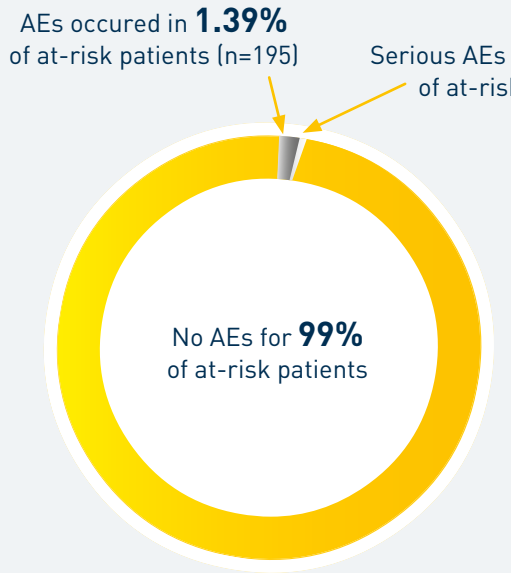
SAFETY OF IOBITRIDOL IN THE GENERAL POPULATION
and at-risk patients

RESULTS

Adverse events (AEs) among all patients
(N=52,057)



Adverse events (AEs) among at-risk patients
(N=14,068)



CONCLUSION

Vogl TJ. *et al*, Eur Radiol. 2006;16(6):1288-1297

SAFETY OF IOBITRIDOL IN THE GENERAL POPULATION
and at-risk patients

Wendt-Nordahl G. *et al*, Med Princ Pract. 2006

INTRAVENOUS CONTRAST MEDIA IN URORADIOLOGY:
Evaluation of Safety and Tolerability in Almost 50,000 Patients

OBJECTIVE

Evaluate the frequency of adverse events and possible risk factors after the administration of **Xenetix®** (iobitridol), an intravenous contrast medium.

METHODOLOGY

- **Large multicenter postmarketing surveillance study**

- **49,975 patients**
undergoing intravenous urography

- **Sex**
Men 56.7%
Women 43.3%

- **Mean age**
56.6 years (3–101)

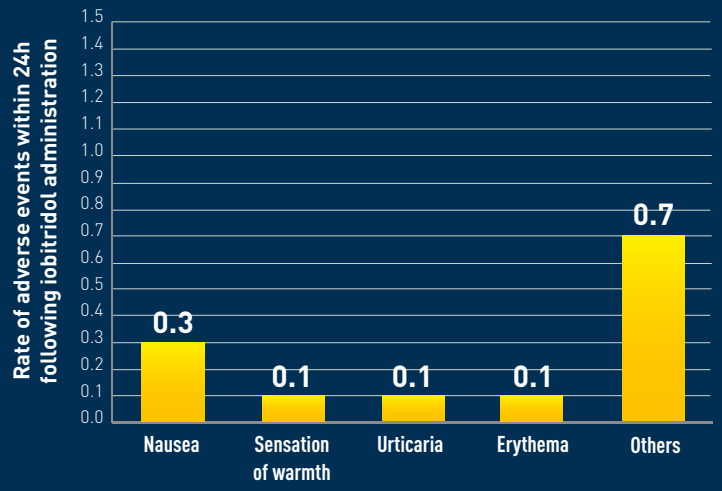
- **High-risk patients**
7.4%
  - Creatinine > 1.5 mg/dl: 1.9%
  - History of previous allergic reactions to CM: 0.8%
  - Pre-existing asthma or allergies: 3.7%
  - Other risk factors: 2%

- **Main indications for urography**
  - Urolithiasis: 39.1%
  - Inflammation: 25.6%
  - Malignancies: 13.9%
  - Others: 24.6%

INTRAVENOUS CONTRAST MEDIA IN URORADIOLOGY:
Evaluation of Safety and Tolerability in Almost 50,000 Patients

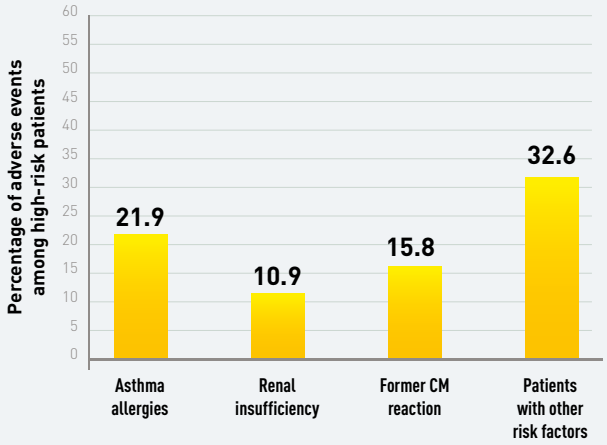
RESULTS

- Only 0.9% of the patients experienced acute adverse events that were non-serious and transient
- The most frequent non-serious events are shown in the graph below



- Less than 0.1% of the patients experienced vomiting, dizziness or cardiovascular problems

- Adverse events were more common in high-risk patients



- The rate of serious adverse events was 0.002%
- Only 1 patient developed an anaphylactic shock but recovered fully under treatment.

INTRAVENOUS CONTRAST MEDIA IN URORADIOLOGY:
Evaluation of Safety and Tolerability in Almost 50,000 Patients

Maurer M. *et al*, Eur J Radiol. 2011;80(2):357-362

SAFETY AND TOLERABILITY OF IOBITRIDOL IN GENERAL AND AT RISK PATIENTS:
Results in more than 160 000 patients

OBJECTIVE

Investigate the safety, tolerability and diagnostic effectiveness of **Xenetix®** (iobitridol) in the general population and at-risk patients.

METHODOLOGY

- **Large postmarketing surveillance study** conducted in Germany between 2002 and 2008

- **160,639 patients**

- **Sex**
  Men 55.1%
  Women 43.6%

- **Mean age**
  58.6 years (5-97)

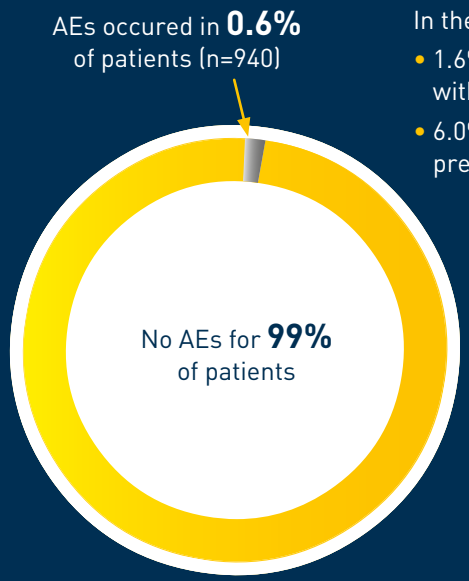
- **High-risk patients**
  - **21.8%** with at least one risk factor
  - **7.3%** with allergies or have previously reacted to contrast medium

- **Pretreatment**
  - **0.7%** of the patients were pretreated (n=1,144)
  - **Significantly more common** in patients with increased risk for an allergic reaction ($p < 0.001$).
  - **Included:** cortisone, H1 or H2 antihistamine, antispasmodic agent, or tranquilizer/sedative.

SAFETY AND TOLERABILITY OF IOBITRIDOL IN GENERAL AND AT RISK PATIENTS:
Results in more than 160 000 patients

RESULTS

Adverse events (AEs) among all patients
(N=160,639)



In these patients:
- 1.6% of AEs occured in patients with allergies
- 6.0% of AEs occured in patients who had previous reactions to contrast medium.

- AEs occurred more in women (0.7% vs. 0.5%; p < 0.001).

Adverse events in high-risk patients with and without treatment

	Pretreated		Not Pretreated	
	No AEs	AEs	No AEs	AEs
Patients with prior allergic contrast medium reaction (n =878)	**95.4%** (n=314)	**4.6%** (n=15)	**93.1%** (n=511)	**6.9%** (n=38)
Patients with asthma/allergies as risk factors (n=11,171)	**97.5%** (n=576)	**2.5%** (n=15)	**98%** (10,419)	**1.5%** (161)

SAFETY AND TOLERABILITY OF IOBITRIDOL IN GENERAL AND AT RISK PATIENTS:
Results in more than 160 000 patients

Gorodetski B. *et al*, Invest Radiol. 2020;55(3):144-152

SAFETY ANALYSIS OF IOBITRIDOL AS A NONIONIC CONTRAST MEDIUM:

A Postmarketing Multicenter Surveillance Study With 94,960 Patients Almost 20 Years After Introduction

OBJECTIVE

Re-evaluate the safety and diagnostic efficacy of **Xenetix®** (iobitridol), a nonionic contrast medium, after almost 20 years of use.

METHODOLOGY

- **Large postmarketing surveillance non-controlled study** conducted in Germany between 2009 and 2013
- **94,960 patients**
- **Sex**
  Men 53.1%
  Women 46.9%
- **Mean age**
  58.8 years
- **High-risk patients**
  30.8%
  with at least 1 risk factor
- **Safety**
  - **Assessed** with standardized questionnaires
  - **Adverse events** gathered and classified according to the System Organ Class and International Conference on Harmonization/Good Clinical Practice guidelines
- **Exam**
  98.2%
  of the population had CT examination or IV urography

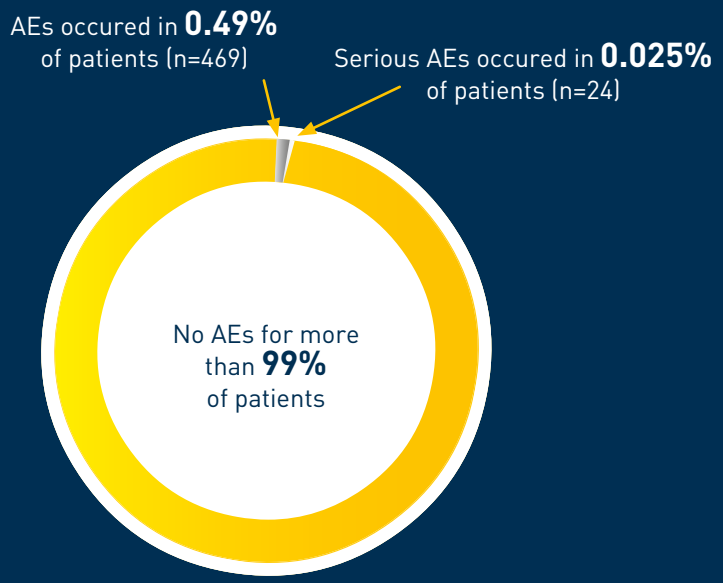
SAFETY ANALYSIS OF IOBITRIDOL AS A NONIONIC CONTRAST MEDIUM:

A Postmarketing Multicenter Surveillance Study With 94,960 Patients Almost 20 Years After Introduction

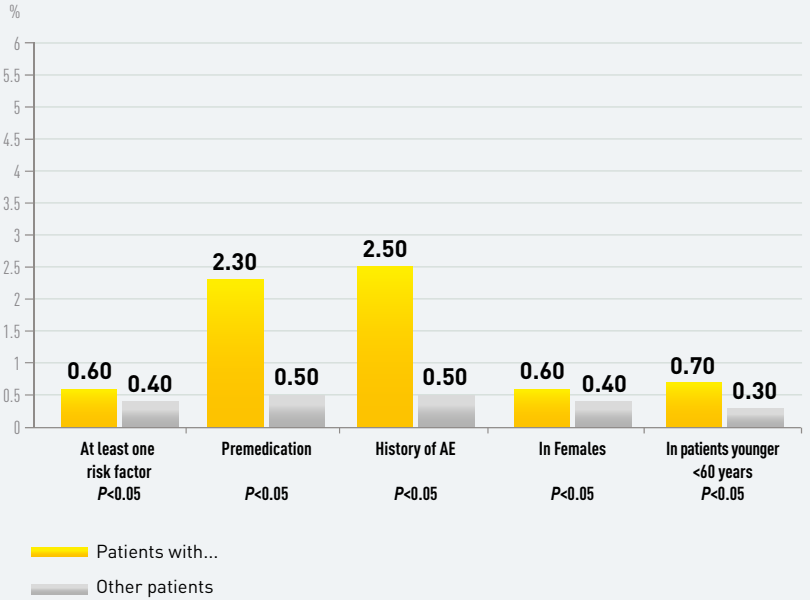
RESULTS

Adverse events (AE) among all patients

(N=94,960)



The prevalence of AEs was significantly higher in some patients



Gorodetski B. *et al*, Invest Radiol. 2020;55(3):144-152

SAFETY ANALYSIS OF IOBITRIDOL AS A NONIONIC CONTRAST MEDIUM:

A Postmarketing Multicenter Surveillance Study With 94,960 Patients Almost 20 Years After Introduction

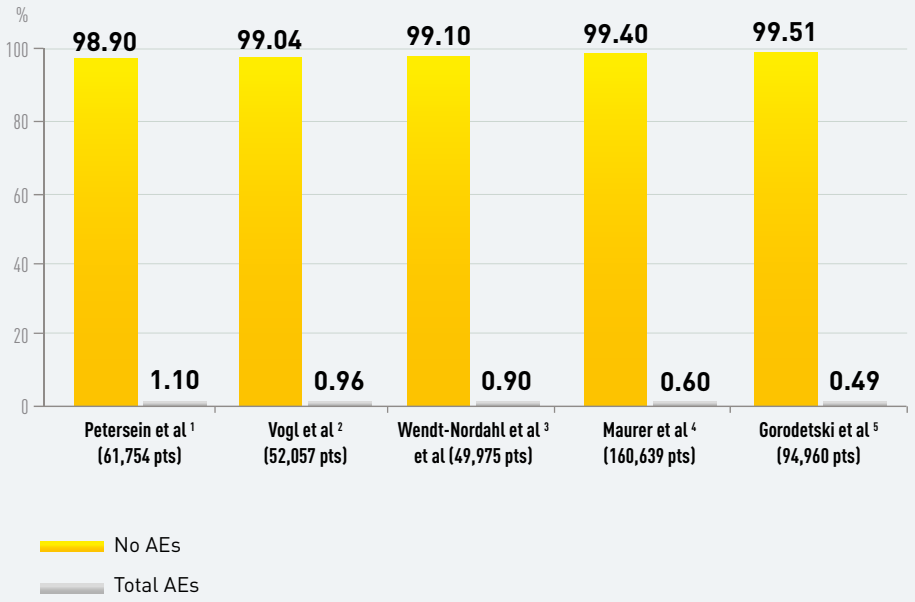
Clinical safety of Xenetix® *(1/3)*

- These five postmarketing studies were conducted in a total of 419,385 patients.[1-5]
- Patients studied were aged between a few weeks and 101 years.[1-5]
- Patients received **Xenetix®** during CT, IV urography, DSA or other examinations.

SAFETY IN THE GENERAL POPULATION

- The majority (99%) of patients included in these five studies did not experience product-related adverse events.[1-5]

Safety profile of Xenetix® in five postmarketing surveillance studies [1-5]*



* Product-related adverse events are shown.
(data from Petersein et al. [1]does not include «feeling of warmth»)

Clinical safety of Xenetix® *(2/3)*

- **The use of Xenetix® was evaluated in a broad range of patient populations.**
- **Xenetix® was found to be well tolerated:**
  - In paediatric population: in one study, 3 patients (4.2%) younger than 15 years of age experienced a total of 3 adverse events: vomiting, nausea and urticaria. None were serious[2]
  - In at-risk patients: in one study, the incidence of adverse events (1.4%) was higher in at-risk patients than in those with no pre-existing risk factors[2]
- **The main risk factors identified in connection with adverse events were:[2]**
  - History of reaction to contrast agents
  - Allergies or asthma
  - Hypotension or hypertension
- **In another postmarketing surveillance study, patients who experienced significantly more adverse events compared to the overall population of patients were:[3]**
  - Patients with asthma/allergies (21.9% of 1,849 patients)
  - Patients with renal insufficiency (defined as creatinine level > 1.5 mg/dL or 133 µmol/L ; 10.9% of 950 patients)

Clinical safety of Xenetix® *(3/3)*

- **In a recent postmarketing study, the prevalence of AEs was significantly higher in:[5]**
  - Patients with at least one risk factor (0.6% vs 0.4%, $p < 0.05$)
  - Patients with a history of AEs after CM administration (2.5% vs 0.5%, $p < 0.05$)
- **In elderly patients, when compared with patients aged ≤ 39 years:**
  - The incidence of adverse events was lower in patients aged ≥ 60 years[1] or ≥ 70 years[2]
  - Respective rates of adverse events were:
    - 0.9% vs. 1.7% ($p < 0.001$ [excluding "feeling of warmth"[1]) in Petersein's study[1]
    - 0.63% vs. 1.40% in Vogl's study[2]
- **In Gorodetski's study, the prevalence of adverse events was higher in patients aged <60 years (0.7%) than ≥ 60 years (0.3%)[5]**
  - This difference was possibly attributable to a higher immunocompetence in younger patients[1]


Overall, the five post-marketing studies concluded that **Xenetix®** **is well tolerated and is safe to use.**

ABOUT Xenetix®

- Its use in medical imaging radiographic procedures is now well established.
- **Xenetix®** is available in a range of concentrations and volumes.
- **Xenetix®** is available in ScanBag®, a unique delivery system, simple to use, safe to handle, practical and designed to achieve optimal asepsis.
- Safety data from 5 large scale postmarketing surveillance studies (more than 400,000 patients included) and from clinical trials show that **Xenetix®** is well tolerated.
- The good renal tolerance of **Xenetix®** has been demonstrated in at-risk patients.

References

1. Petersein J., et al., Results of the safety and efficacy of iobitridol in more than 61,000 patients. Eur Radiol, 2003. 13(8): p. 2006-2011. *Methodology: 61,754 patients undergoing routine examination (CT, IVU, DSA, conventional angiography and phlebography). Patients aged from a few weeks to 97 years.*

2. Vogl T.J., et al., Safety of iobitridol in the general population and at-risk patients. Eur Radiol, 2006. 16(6): p. 1288-1297. *Methodology: 52,057 patients undergoing routine examination (CT, IVU, DSA, conventional angiography and phlebography). Patients aged from 4 to 98 years with 72 patients less than 15 years of age and 28549 patients aged 60 and above Pre-existing risk factors were present in 27% of patients).*

3. Wendt-Nordahl G., et al., Intravenous contrast media in uroradiology: Evaluation of safety and tolerability in almost 50,000 patients. Med Princ Pract, 2006. 15(5): p. 358-361. *Methodology: 49,975 patients undergoing IVU (98 %) or other urological examinations (2 %). Patients aged from 3 to 101 years. Patients were considered at high risk for 7.4% of the total recruitment.*

4. Maurer M., et al., Safety and tolerability of iobitridol in general and in patients with risk factors: results in more than 160,000 patients. Eur J Radiol, 2011. 80: p. 357-62. *Methodology: 160,639 patients undergoing routine examination (IVU, CT). Patients aged from 5 to 97 years. At least one risk factor was reported in 21.8% of patients.*

5. Gorodetski B., et al., Safety Analysis of Iobitridol as a Nonionic Contrast Medium: A Postmarketing Multicenter Surveillance Study With 94,960 Patients Almost 20 Years After Introduction. Invest Radiol, 2020. 55(3): p. 144-152. *Methodology: 94,960 patients undergoing routine examination (CT,IVU, phlebography, angiography, and angiocardiography). At least one risk factor was reported in 30.8% of patients.*

Xenetix®
Iobitridol

(*) For complete information please refer to the local Summary of Product Characteristics

(**) Indications, volumes and presentations may differ from country to country.

www.guerbet.com

Xenetix® is part of UNIK, our interconnected solutions for Diagnostic Imaging

UNIK
Tailored interconnected solutions driving your journey to excellence

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, whole body and cranial computed tomography, intravenous digital subtraction angiography, arteriography, angiocardiography, Sialography, Endoscopic retrograde cholangiopancreatography – **Xenetix® 300:** intravenous urography, whole body and head computed tomography, intravenous digital subtraction angiography, arteriography, angiocardiography, endoscopic retrograde cholangiopancreatography, arthrography, hysterosalpingography, herniography – **Xenetix® 250:** phlebography, whole body computed tomography, intra-arterial digital subtraction angiography, arteriography, 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 (*): There is a risk of allergic reactions regardless of the route of administration or the dose. 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 - Before administering an iodinated contrast agent, it is important to ensure that the patient is not scheduled to undergo a scintigraphic examination or laboratory tests related to the thyroid or to receive radioactive iodine for therapeutic purposes. Administration of contrast agents via any route disrupts hormone concentrations and iodine uptake by the thyroid or by metastases of thyroid cancer, until urine iodine levels have returned to normal. Extravasation is a non-exceptional complication (0.04% to 0.9%) of intravenous injections of contrast media. More frequent with the high osmolar products, most of the injuries are minor, however severe injuries such as skin ulceration, tissue necrosis, and compartment syndrome may occur with any iodinated contrast medium. The risk and/or severity factors are patient-related (poor or fragile vascular conditions), and technique-related (use of a power injector, large volume). It is important to identify these factors, optimize the injection site and technique accordingly, and monitor the injection prior to, during and after the injection of Xenetix® –
Special warnings and precautions for use (*): For at risk patients with:1) Intolerance to iodinated contrast agents: Prior the examination, at-risk patients should be identified by a precise screening of histories. During the procedure, the medical surveillance and permanent venous access must be maintained. After the examination the patient must be monitored for at least 30 minutes, since most serious adverse reactions occur within this time period and the patient must be informed of the possibility of delayed reactions (for up to seven days), 2) Severe cutaneous adverse reactions: At the time of initiation patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. Xenetix should be discontinued immediately upon suspicion of a severe hypersensitivity reaction. If the patient has developed a severe cutaneous adverse reaction with the use of Xenetix®, Xenetix® must not be re-administered in this patient at any time, 3) Renal insufficiency and/or hepatic insufficiency: Care should be taken in renal or hepatic impairment, diabetes or in patients with sickle cell disease, adequate hydration should be ensured in all patients before and after contrast media administration and particularly in patients with renal impairment or diabetes. 4) Asthma: Stabilisation of asthma is recommended before the injection of an iodinated contrast agent. Due to an increased risk of bronchospasm, special caution should be taken in patients do to suffered an asthmatic attack within eight days prior to the examination. 5) Dysthyroidism: After iodinated contrast agent injection, particularly in patients with a goitre or a history of dysthyroidism, there is a risk either of a flare-up of hyperthyroidism or development of hypothyroidism. There is also a risk of hypothyroidism in neonates who have received, or whose mother has received, an iodinated contrast agent. Therefore, thyroid function in such neonates should be evaluated and closely monitored to ensure thyroid function is normal. 6) Cardiovascular diseases: Careful weighing up of the risk-benefit ratio is necessary in these patients. 7) Central nervous system disorders: The benefit-to-risk ratio must be evaluated for each case: due to the risk of aggravation of neurological symptoms in patients with a transient ischaemic attack, acute cerebral infarct, recent intracranial haemorrhage, cerebral oedema, or idiopathic or secondary (tumour, scar) epilepsy and if the intra-arterial route is used in an alcoholic patient (acute or chronic alcoholism) and other drug-addicted subject. 8) Pheochromocytoma: Patients with pheochromocytoma may develop a hypertensive crisis after intravascular administration of a contrast agent and must be monitored prior to the examination. 9) Myasthenia: Administration of a contrast agent may worsen the symptoms of myasthenia gravis.10) Intensification of side effects: Adverse reactions related to iodinated contrast agent administration may be intensified in patients showing pronounced agitation, anxiety and pain. Appropriate management such as sedation may be necessary.

Xenetix®
lobitridol

(*) For complete information please refer to the local Summary of Product Characteristics

(**) Indications, volumes and presentations may differ from country to country.

Warnings and precautions for use specific to certain administration routes with appreciable systemic diffusion (*): - Products administered via the intra-uterine route (Xenetix® 300): Contraindication: Pregnancy for hysterosalpingography-Special precautions for use: In the interview and with appropriate tests, systematically check for possible pregnancy in women of childbearing age. Exposure of the female genital routes to x-rays must be subject to careful evaluation of the benefit-to-risk ratio. In the event of inflammation or acute pelvic infection, hysterosalpingography can only be performed after a careful assessment of the benefit-to-risk ratio. - Risk of acute pancreatitis in the context of endoscopic retrograde pancreatography **-Interaction with other medicinal products and other forms of interaction (*):** beta-blocker substances, diuretics, metformin, radiopharmaceuticals, interleukin 2
Fertility, pregnancy and lactation (*)
Undesirable effects(*): Uncommon (≥1/1000 to <1/100): nausea, feeling hot - Rare (≥ 1/10 000 to <1/1 000): hypersensitivity, presyncope, tremor, paresthesia, vertigo, tachycardia, bradycardia, hypotension, dyspnoea, cough, throat tightness, sneezing, vomiting, angioedema, urticaria, erythema, pruritus, facial oedema, malaise, chills, injection site pain - Very rare (<1/10 000): anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, thyroid disorder, coma, seizure, confusional state, visual pathway disorders, amnesia, photophobia, blindness transient, somnolence, agitation, headache, hypoacusis, cardiac arrest, myocardial, infarction (more frequent after intracoronary injection), arrhythmia, ventricular fibrillation, angina pectoris, torsades de pointes, coronary arteriospasm, circulatory collapse, respiratory arrest, pulmonary oedema, bronchospasm, laryngospasm, laryngeal oedema, abdominal pain, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, eczema, rash maculo-papular (all as delayed hypersensitivity reactions), acute kidney injury, anuria, injection site necrosis following extravasation, injection site inflammation following extravasation, injection site oedema, blood creatinine increased - Not known: transient neonatal hypothyroidism, dizziness, cyanosis, hypertension, drug reaction with eosinophilia and systemic symptoms (DRESS) - Compartment syndrome may be observed following extravasation
Overdose (*) – Pharmacodynamic properties (*): Pharmacotherapeutic group: Water-soluble, nephrotropic radiology 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:** January 2021.

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.

www.guerbet.com

Xenetix® is part of UNIK, our interconnected solutions for Diagnostic Imaging

UNIK
Tailored interconnected solutions driving your journey to excellence

P21000842 – February 2022