SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TELEBRIX 12 SODIUM , solution for injection for intravesical administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For 100 mL of solution:

Sodium ioxitalamate ..... 21.00 g
Equivalent to iodine ..... 12 g

- Iodine content per mL: 120 mg
- Iodine mass per 250 mL bottle: 30g

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for intravesical administration

- Viscosity at 20°C: 1.7 mPa.s
- Viscosity at 37 °C: 1.1 mPa.s
- Osmolality: 640 mOsm / kg

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For diagnostic use only.

Contrast medium for:
- Retrograde cystography;

4.2 Posology

Indications	Average dose mL/kg	Total volume (min.-max.) mL
Retrograde cystography	Dose to be adapted to the volume of the organ to be injected	20 - 100

Method of administration
The product must be administered by intravesical administration only

4.3 Contraindications

- Hypersensitivity to ioxitalamic acid or to any of the excipients listed in section 6.1
- History of major immediate or delayed skin reaction (see section 4.8) to Telebrix 12 Sodium Intra-vascular administration.
- Intra-vascular administration
- Manifest thyrotoxicosis

- Intrathecal or subarachnoid (or epidural) administration of TELEBRIX 12 Sodium for myelography, cerebral ventriculography or cisternography is contraindicated as severe and potentially life-threatening neurotoxic reactions (e.g. myoclonus or epilepsy) can occur

4.4. Special warnings and precautions for use

- There is a risk of allergy, whatever the administration route or dosage.
- The risk of intolerance cannot be ruled out when medicinal products are administered locally to opacify body cavities:

a) administration via certain routes (e.g. articular, biliary, intrathecal, intra-uterine) results in considerable systemic diffusion so systemic effects may occur.

b) oral or rectal administration usually results in a very limited systemic diffusion. If the gastrointestinal mucosa is healthy, no more than 5% of the administered dose passes into the urine, the rest being excreted in the faeces. However, when the gastrointestinal mucosa is damaged, absorption is increased. Where the gut is perforated, the entire dose may pass rapidly into the peritoneal cavity, to be eliminated in the urine. The onset of any dose-related, systemic effect is therefore related to the integrity of the gastrointestinal mucosa.

c) the immuno-allergic mechanism, however, is not dose-related and may be involved, whatever the route of administration.

Hence, the frequency and intensity of undesirable effects differ for:

- medicinal products administered via the intra-vascular and certain topical routes,
- medicinal products administered via the gastrointestinal route and only slightly absorbed under normal conditions.

4.4.1. Special Warnings

4.4.1.1 Hypersensitivity

All iodinated contrast medium can cause minor or major reactions that may be life-threatening. They may be immediate (less than 60 minutes) or delayed (up to 7 days). They are often unpredictable.

The risk of major reaction requires the immediate availability of the means necessary for emergency resuscitation.

Several mechanisms have been reported:
- Direct toxicity affecting the vascular endothelium and tissue proteins.
- Pharmacological action altering the concentration of certain endogenous factors (histamine, complement fractions, inflammation mediators), more frequent with hyperosmolar products.
- Immediate IgE-mediated allergy (anaphylaxis) to TELEBRIX 12 SODIUM (120 mg I/mL), solution for intravesical administration.
- Cell-mediated allergic reactions (delayed skin reactions).

Patients having previously suffered a reaction during administration of an iodinated contrast medium are at increased risk of experiencing a renewed reaction during administration of the same, or another iodinated contrast medium, and are therefore considered to be high risk subjects.

4.4.1.2 Iodinated contrast media and the thyroid (see also section 4.4.2.35. Precautions for use - Dysthyroidism)

Before administering iodinated contrast media, it is recommended to make sure that the patient is not to undergo thyroid scintigraphy or laboratory tests, or to receive any radioactive iodine for therapy.

Iodinated contrast media, whatever the administration route, may interfere with hormone assays and iodine binding within the thyroid gland and thyroid cancer metastases until urine levels of iodine return to normal. Since thyroid tests are altered, they should be performed prior to radiological examinations. If tests are necessary in the weeks following the administration of an iodinated contrast medium, thyroid hormones (thyroxine, triiodothyronine) should be assayed directly.

4.4.2. Precautions for use

4.4.2.1. Intolerance to iodinated contrast media:
Before the examination:

- identify high-risk patients by conducting an interview focusing on medical history.

Corticosteroids and histamine H1-antagonists have been proposed for premedicating patients at the highest risk of hypersensitivity.However, this alone cannot entirely preclude a serious reaction, including serious or fatal anaphylactic shock. During the examination, it is important to:

  - monitor the patient closely.
  - maintain venous access.
  - have drugs and equipment for resuscitation readily available

After the examination:

- after the contrast medium has been administered, the patient must be monitored closely for at least 30 minutes as most serious undesirable effects occur within that period.
- the patient must be warned of the possibility that allergic reactions may occur after some delay (up to 7 days) (see section 4.8 Undesirable effects).

The following precautions for use must be considered if the integrity of the bladder wall cannot be confirmed before product administration:

4.4.2.2. Asthma
It is preferable to control asthma well before administering an iodinated contrast medium.

Special care is necessary where the patient has suffered an asthma attack in the eight days prior to the examination, as this exacerbates the risk of bronchospasm.

4.4.2.3. Dysthyroidism
An administration of iodinated contrast media may cause episodes of hyperthyroidism or may induce hypothyroidism, particularly in patients presenting with goitre, or with a history of dysthyroidism. Hypothyroidism may also occur in neonates who have received, or whose mothers received, an iodinated contrast medium. Their thyroid function should be therefore evaluated and monitored.

4.4.2.4. Central nervous system disorders
The benefit/risk ratio must be assessed case-by-case:

- due to the risk of aggravating neurological symptoms in patients suffering a transient ischaemic attack, acute cerebral infarction, recent intra-cranial haemorrhage, cerebral oedema, idiopathic or secondary (tumour, scar) epilepsy.

4.4.2.5. Pheochromocytoma

Patients with pheochromocytoma may suffer an attack of hypertension after intra-vascular administration of contrast media and suitable management should be implemented before the examination.

4.4.2.6. Myasthenia

Administration of a contrast medium may worsen myasthenia symptoms.

4.4.2.7 Exacerbation of side effects

The undesirable effects of iodinated contrast media may be exacerbated by excitement, anxiety or pain. Suitable management, including sedation, may be required.

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

4.5.1. Medicinal products

- **Radiopharmaceuticals** (see also section 4.4.1. Special Warnings)

  Iodinated contrast media disturb the uptake of radioactive iodine by thyroid tissue for several weeks, and this may result in poor binding during thyroid scintigraphy and may reduce the efficacy of 131-iodine treatment.

  If the patient is to undergo renal scintigraphy by injecting a radiopharmaceutical product secreted by the renal tubule, it is preferable to conduct such an examination prior to the injection of a contrast medium.

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

  These drugs reduce the efficacy of cardiovascular mechanisms that compensate for blood pressure disorders.

  Hypersensitivity reactions can be aggravated in patients on beta-blockers, and particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment of hypersensitivity reactions with beta-agonists.

  The physician must be informed prior to injecting a contrast medium and must have resuscitation equipment at hand.

- **Interleukin 2**

  Treatment with interleukin 2 (iv route) may exacerbate any reaction to contrast media: i.e. rash, flushing, erythema, fever or flu-like symptoms or,more rarely, hypotension, oliguria or even renal failure.

4.5.2. Other forms of interaction

High concentrations of iodinated contrast media in plasma and urine may interfere with *in vitro* assays of bilirubin, proteins and inorganic substances (iron, copper, calcium and

phosphate). It is therefore recommended to avoid such assays in the 24 hours following the examination:
Thyroid function, thyroid tests (see section 4.4.1.2 Special warnings - Iodinated contrast media and the thyroid, and section 4.4.2.5. Precautions for use - Dysthyroidism).

4.6. Fertility, pregnancy and lactation

Pregnancy

Since radiation exposure during pregnancy should be generally avoided, regardless of whether a contrast agent is used or not, the benefit of X-ray examination has to be considered carefully.

Embryotoxicity

Animal studies have not revealed any teratogenic effect.

In view of this, no malformative effect is expected in man. To date, substances causing malformation in man have been found to be teratogenic in animals during well-conducted studies on two species.

Foetotoxicity

The short-term iodine overload after the administration of a contrast medium to a pregnant mother may cause foetal dysthyroidism, should the examination be carried out after the 14th week of amenorrhoea. The thyroid function of neonates exposed in utero should be evaluated and monitored. However, the reversibility of the effect, and the expected benefit for the mother, justify the single administration of an iodinated contrast medium where a radiological examination of a pregnant woman is necessary.

Fertility

Reproductive toxicology studies did not reveal an effect on reproduction, fertility or fœtal and post-natal development.

Lactation

Only small quantities of iodinated contrast media are secreted into breast milk. There is therefore little risk of a single administration to mothers causing undesirable effects in the infants. It is preferable to discontinue breast-feeding for 24 hours after the administration of an iodinated contrast medium.

4.7. Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Due to the pharmacological properties of TELEBRIX 12 SODIUM itself, an effect on the ability to drive and use machines is unlikely.

4.7. Undesirable effects

Since post-marketing, the most commonly reported adverse reactions following the administration of TELEBRIX (any form) are hypersensitivity (including anaphylactic reaction, anaphylactoid reaction and anaphylactic shock), urticaria, rash (including erythema and maculo-papular rash) and injection site reactions (such as oedema, pain and inflammation).

The hypersensitivity reactions are usually immediate (during the administration or over the hour following the start of the administration) or sometimes delayed (one hour to

several days after the administration), and then appear in the form of adverse skin reactions.

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

The adverse reactions are listed in the table below by SOC (System Organ Class) and with frequency as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

Tabulated list of adverse reactions reported with TELEBRIX 12 Sodium or another form of TELEBRIX following intravesical administration:

System Organ Class	**Frequency: Adverse reaction**
Immune system disorders	Frequency not known: Anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity
Endocrine disorders	Frequency not known: Thyrotoxic crisis*, hyperthyroidism*, thyroid disorder**
Nervous system disorders	Frequency not known: Syncope, convulsion, tremor, dizziness, headache
Cardiac disorders	Frequency not known: Tachycardia
Vascular disorders	Frequency not known: Hypotension
Respiratory, thoracic and mediastinal disorders	Frequency not known: Laryngeal oedema, pulmonary oedema, dyspnoea, cough
Gastrointestinal disorders	Frequency not known: Diarrhoea, nausea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Frequency not known: *Immediate:* Angioedema, urticaria, pruritus, erythema, hyperhidrosis *Delayed:* Rash, rash maculo-papular
Renal and urinary disorders	Frequency not known: Renal failure acute, anuria
General disorders and administration site conditions	Frequency not known: Oedema, face oedema, pain, malaise, feeling hot, pyrexia, chills
Investigations	Frequency not known: Blood creatinine increased

*Thyrotoxicosis may occur in patients with asymptomatic or uncontrolled hyperthyroidism as well as in patients with autonomous thyroid nodules (take special care with elderly patients). The occurrence of symptoms may be delayed (for several months) after the administration.

****** Thyroid disorder may be the exacerbation of a goitre. Temporary hypothyroidism may also occur in newborns (premature infants) that have received, or whose mother has received an iodinated contrast medium.

The following adverse reactions were reported with any form of TELEBRIX following non-intravesical administration and/or with other iodinated contrast media:

System Organ Class	Adverse reaction
Psychiatric disorders	Confusional state, hallucination, agitation, anxiety
Nervous system disorders	Coma, brain oedema, loss of consciousness, paresis/paralysis, paraesthesia, amnesia, speech disorder, somnolence, dysgeusia
Eye disorders	Visual impairment, photophobia, blindness transient, eyelid oedema
Ear and labyrinth disorders	Vertigo, hearing impaired
Cardiac disorders	Cardiac arrest, myocardial infarction, angina pectoris, arrhythmia, bradycardia, cyanosis
Vascular disorders	Shock, hypertension, thrombophlebitis[1], flushing, pallor
Respiratory, thoracic and mediastinal disorders	Respiratory arrest, respiratory failure, pneumonia aspiration[2], laryngospasm, bronchospasm, throat tightness, sneezing
Gastrointestinal disorders	Pancreatitis[3], ileus[4], enterocolitis[4], parotid gland enlargement, salivary hypersecretion
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, eczema, dermatitis bullous[1]
Musculoskeletal and connective tissue disorders	Arthralgia[5], muscle spasms
Reproductive system and breast disorders	Pelvic pain
General disorders and administration site conditions	Injection site extravasation, injection site pain, injection site inflammation, injection site oedema, injection site necrosis [6]
Investigations	Electroencephalogram abnormal, blood amylase increased

[1] following intravascular administration
[2] in patients with swallowing impairment, oral route
[3] following endoscopic retrograde cholangiopancreatography (*ERCP*)
[4] following enteral administration
[5] in the event of arthrography
[6] in the event of extravasation

Adverse reactions in children
The expected nature of the undesirable effects connected with TELEBRIX 12 SODIUM is the same at that of the effects reported in adults. Their frequency cannot be estimated from the available data.

4.9. Overdose

Toxicity from overdose of TELEBRIX 12 SODIUM is unlikely due to the intravesical administration.

Overdose increases the risk of nephropathy and can result in diarrhoea, dehydration, electrolyte imbalance, haemodynamic and cardiovascular disorders.

With very high doses, fluid and electrolyte losses must be compensated by appropriate rehydration. Renal function must be monitored during at least three days. Haemodialysis may be carried out if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: IODINATED CONTRAST MEDIUM (V: miscellaneous)
ATC Code: V08AA05

TELEBRIX 12 SODIUM (120 mg I/mL), solution for intravesical administration, is a hydrosoluble, ionic contrast medium (640 mOsm/kg).

5.2. Pharmacokinetic properties

After intravesical administration, ioxitalamic acid is excreted rapidly, in unchanged form, in the urine.

5.3. Preclinical safety data

Effects have only been observed in animals at a level of exposure significantly higher than the maximum dose in humans, and are therefore of little clinical significance.

6. PHARMACEUTICAL DATA

6.1 List of excipients

Sodium hydroxide, sodium calcium edetate, sodium dihydrogen phosphate dihydrate, water for injection.

6.2. Incompatibilities

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

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 25ºC. Keep protected from light.

6.5. Nature and contents of container

250 mL colourless glass bottle (type II) with an elastomer stopper (chlorobutyl).

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

GUERBET
BP 57400
95943 ROISSY CDG CEDEX
FRANCE

8. REGISTRATION HOLDER:

Promedico Ltd.
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