הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: **28/07/2011**

שם תכשיר באנגלית: **Telebrix 12 sodium**

מספר רישום : **26111**

שם בעל הרישום : **Promedico Ltd.**

פרטים על השינוי/ים המבוקש/ים

טקסט חדש	טקסט נוכחי	פרק בעלון
• 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	• Hypersensitivity to ioxitalamic acid or to any of the excipients; • History of major immediate or delayed skin reaction (see section 4.8) to Telebrix 12 Sodium (120 mg iodine/mL), solution for injection; • Decompensated heart failure, when used by systemic injection; • Endoscopic retrograde pancreatography (ERP) for acute pancreatitis; • Overt thyrotoxicosis; Myelography	**4.3 Contraindications**
4.4.1. Special Warnings 4.4.1.1 Hypersensitivity ~~Any~~ 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.	*4.4.1.2.1. Intolerance to iodinated contrast media:* Prior to the examination: • Identify subjects at risk via specific questioning concerning history. Corticosteroids and H1-antihistamines were suggested as premedication in patients at the highest risk of intolerance reaction (known to be intolerant to an iodinated contrast medium). However, they do not prevent serious or fatal anaphylactic shock to occur. During the examination, the following must be ensured: ▪ Medical supervision ▪ Maintenance of a venous access.	**4.4 Special warnings and precautions for use**

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. <u>4.4.1.2 Iodinated contrast media and the thyroid (see also section 4.4.2.35. Precautions for use - Dysthyroidism)</u> 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.	After the examination: • Further to administration of a contrast medium, the patient must remain under observation for at least 30 minutes, as most adverse effects occur within this time. • The patient must be warned that late onset reactions may occur (up to 7 days later) (see section 4.8). <u>*4.4.1.2.2. Renal failure*</u> Iodinated contrast media may temporarily alter renal function or aggravate existing renal failure. The preventive measures to be taken are as follows: • Identify high risk patients: dehydrated subjects, patients with renal failure, diabetes, severe heart failure, monoclonal gammapathy (multiple myeloma, Waldenström's disease) or a history of renal failure following administration of iodinated contrast media, children under one year and atheromatous elderly subjects. • Initiate appropriate hydration by fluid and sodium solution where required. • Avoid combinations of nephrotoxic medicines (if such combinations are necessary, reinforce renal biological monitoring). The medicinal products in question are notably aminoglycosides, organoplatins, high-dose methotrexate, pentamidine, foscarnet and certain antivirals (aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, and tenofovir), vancomycin, amphotericin B, immunosuppressants such as ciclosporine or tacrolimus, ifosfamide. • Allow for a 48-hour interval between two X-ray examinations involving injection of an iodinated contrast medium, or defer any further examinations until after initial renal function has been restored. • Prevent lactic acidosis in diabetic patients treated with metformin, according to blood creatinine levels. Normal renal function: administration of metformin should be interrupted for at least 48 hours as the iodinated contrast medium is administered, or until normal renal function is restored. Abnormal renal function: metformin is contraindicated. In an emergency: if the examination is required, precautions must be taken: interruption of metformin treatment, hydration, monitoring of renal function and detection of symptoms of lactic acidosis.	

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 injecting 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 injection 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.

Haemodialysis patients may receive iodinated contrast media as these products are dialysable. The haemodialysis department must first be consulted.

4.4.1.2.3. Liver failure
Special attention must be paid when a patient suffers both from liver failure and renal failure, as this situation increases the risk of contrast medium retention.

4.4.1.2.4. Asthma
Asthma must be stabilized prior to injection of an iodinated contrast medium.
Special attention must be paid in cases of asthma attacks occurring 8 days prior to the examination, due to the increased risk of bronchospasm.

4.4.2.1.5. Dysthyroidism
Following injection of an iodinated contrast medium, in particular in patients with goitre or with a history of dysthyroidism, the risk of hyperthyroidism or induction of hypothyroidism also exists. Hypothyroidism may also occur in newborns that have received, or whose mother has received an iodinated contrast medium.

4.4.1.2.6. Severe cardiovascular disease
In the event of existing or early stage heart failure, coronary artery disease, pulmonary arterial hypertension or valvular heart disease, the risk of pulmonary oedema, myocardial ischemia and arrhythmia or severe hemodynamic disorders is increased following administration of an iodinated contrast medium.

4.4.1.2.7. Central nervous system disorders
The benefit/risk ratio must be estimated on a case per case basis:

- due to the risk of worsening of neurological symptoms in patients presenting with transient ischemic attack, acute cerebral infarction, recent intracranial haemorrhage, and cerebral oedema, idiopathic or secondary epilepsy (tumour, scar).
- during use by intra-arterial route in alcoholics (acute or chronic alcoholism) and users of other drugs.

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 contrast media may exacerbate the 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.	*4.4.1.2.8. Phaechromocytoma* Patients suffering from phaechromocytoma may experience hypertension surge following intravascular administration of a contrast medium and may require appropriate treatment prior to the procedure. *4.4.1.2.9. Myasthenia* Administration of a contrast medium may worsen myasthenia symptoms. *4.4.1.2.10. Enhanced side effects* Side effects related to administration of iodinated contrast media may be enhanced by pronounced states of excitation, anxiety and pain. Appropriate treatment, and possibly sedation, may be necessary.	
• 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	**4.5.1. Medicinal products** • **Metformin in diabetics** (see section 4.4.1.2.2. Precautions for use – Renal Failure). • **Radiopharmaceuticals** (see section 4.4.1. Special Warnings) Iodinated contrast media disturb radioactive iodine uptake by thyroid tissue during several weeks, and this may lead to poor fixation in the thyroid scintigraphy and reduced effectiveness of iodine 131 treatment. Where renal scintigraphy performed by injection of renal tubular secreted radiopharmaceuticals is planned, it is recommended to carry out this procedure prior to injection of the iodinated contrast medium. • **Beta-blockers,** vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists. These medicinal products lead to a reduction in the effectiveness of cardiovascular compensation mechanisms in blood pressure disorders: The doctor must be informed if the patient is taking such treatment prior to injection of the iodinated contrast medium and have the necessary	**4.5. Interaction with other medicinal products and other forms of interaction**

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).	resuscitation means at hand. • **Diuretics** Due to the risk of dehydration induced by diuretics, fluid and electrolyte rehydration is initially necessary for minimizing the risk of acute kidney failure. • **Interleukin-2** Enhanced reaction to contrast media during treatment with interleukin-2 (intravenous route) may occur: rash or more rarely hypotension, oliguria or even kidney failure.	

4.8. 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. Fertility, pregnancy and lactation** **Embryotoxicity** Studies conducted in animals have not shown any teratogenic effects. In the absence of teratogenic effects in animals, no malformation in humans is expected. To date, the substances causing malformations in humans have been found to be teratogenic in animals in well conducted studies in two species. **Foetotoxicity** Occasional iodine overload following administration of the medium in the mother may lead to foetal dysthyroidism if the examination is carried out after 14 weeks' amenorrhea. However, reversibility of this effect and the expected maternal benefit indicate that occasional administration of an iodinated contrast medium should not be delayed where the indication for radiological examination in pregnant women is carefully assessed. **Fertility** Toxicological studies conducted on reproduction function did not show any effects on reproduction, fertility or foetal or post-natal development. **Breastfeeding** Small quantities of iodinated contrast media are excreted in breast milk. Occasional administration in mothers therefore bears a low risk of causing adverse effects in infants. It is advisable to suspend breastfeeding for 24 hours following administration of an iodinated contrast medium.	**4.6. Fertility, pregnancy and lactation**
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.	Not applicable.	**4.7. Effects on the ability to drive and use machines**
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	An adverse reaction is said to be: • very common if its frequency is ≥ 10 % • common if its frequency is ≥ 1% and < 10% • uncommon if its frequency is ≥ 0.1% and < 1%	**4.8. Undesirable effects**

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

- rare if its frequency is ≥ 0.01% and < 0.1 %
- very rare if its frequency is < 0.01%

4.8.1. Anaphylactoid and hypersensitivity reactions

Hypersensitivity reactions, including anaphylactic or anaphylactoid reactions, possibly leading to death, include one or more of the following effects:

4.8.1.1. Skin and subcutaneous tissue (very rare):

- Immediate: pruritus, erythema, localised or extensive urticaria, facial oedema, angioedema.
- Late onset: maculopapular exanthema, and in exceptional cases: Stevens-Johnson syndrome or Lyell's syndrome.

Not reported with TELEBRIX 12 SODIUM (120 mg I/mL), solution for injection: eczema, erythema multiforme.

4.8.1.2. Respiratory (very rare):

Cough, feeling of tightening of the throat, dyspnoea, bronchospasm, laryngeal oedema, laryngospasm, respiratory arrest.

Not reported with TELEBRIX 12 SODIUM (120 mg I/mL), solution for injection: sneezing fits.

4.8.1.3. Cardiovascular (very rare):

- Hypotension, vertigo, faintness, tachycardia, cardiac arrest.

Not reported with TELEBRIX 12 SODIUM (120 mg I/mL), solution for injection: bradycardia.

4.8.1.4. Other events (very rare):

Nausea, vomiting, abdominal pain.

4.8.2. Other undesirable effects

4.8.2.1. Cardiovascular (very rare)

- Vagal syncope, arrhythmia, angina, myocardial infarction, more common in the case of intracoronary injection.
- Cardiovascular collapse of varying seriousness that may occur abruptly with no warning signs, or complicate the cardiovascular symptoms described above.
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4.8.2.2. Neurosensory (very rare)

- Systemic administration: sensation of warmth. Headache
- Examinations during which the iodinated contrast medium is

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	Stevens-Johnson syndrome, toxic epidermal

found at high levels in the cerebral arterial blood: agitation, confusional state, tremor, paresthesiae, paresis/paralysis, convulsion, coma.
Not reported with TELEBRIX 12 SODIUM (120 mg I/mL), solution for injection: hallucinations, amnesia, speech disorders, visual disturbances (photophobia, transient blindness), hearing disorders, minor EEG alterations, drowsiness.

4.8.2.3. Gastro-intestinal (very rare)

- Nausea, vomiting.
- Abdominal pain and diarrhoea, especially related to administration via upper or lower gastro-intestinal route.

Not reported with TELEBRIX 12 SODIUM (120 mg I/mL), solution for injection: parotid hypertrophy subsequent to the examination, hypersalivation, transient taste disorders, increased serum amylase levels, due to the injection pressure, and, rarely, acute pancreatitis following ERCP.

4.8.2.4. Respiratory (very rare)
Pulmonary oedema.

4.8.2.5. Renal (see section 4.4)
Transient increase in blood creatinine levels may be observed but anuric acute renal failure is very rare.

4.8.2.6. Thyroid (see sections 4.4 and 4.5)

4.8.2.7. Local effects (very rare)

- Transient, benign local oedema and pain may occur at the injection site in the absence of extravasation of the product injected. By intra-arterial administration, the painful sensation at the injection site depends on the osmolality of the product injected. In the event of extravasation **(<** 0.01%**),** local inflammatory reaction or even tissue necrosis may be observed.
- Thrombophlebitis

Not reported with TELEBRIX 12 SODIUM (120 mg I/mL), solution for injection: joint pain in the event of arthrography.

	tissue disorders	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 <u>Adverse reactions in children</u> 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.				
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.		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.		**4.9.Overdose**