הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 6.2013

שם תכשיר באנגלית ומספר הרישום: Telebrix 35 Meglumine (054-38-26112-00)

שם בעל הרישום: Promedico LTD

השינויים בעלון מסומנים על רקע צהוב

טופס זה מיועד לפרוט ההחמרות בלבד !

פרטים על השינוי/ים המבוקש/ים		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
2. Qualitative and quantitative composition		Excipient with known effect: Sodium (341.8 mg sodium per 100 mL).

Special populations *Elderly patients* TELEBRIX 35 should be administered with caution (see section 4.4), in well-hydrated patients at the minimum effective dose. *Patients with renal impairment* In patients with renal failure, the dose is reduced and sufficient hydration must be ensured (see also section 4.4.2.2. Precautions for use – Renal failure). **Method of administration** The product must be administered via intra-arterial or intravenous route.		**4.2 Posology and method of administration**
• 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 35 injection • Decompensated heart failure • Manifest thyrotoxicosis • Intrathecal or subarachnoid (or epidural) administration of TELEBRIX 35 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 35 ; • Decompensated heart failure by systemic injection; • Overt thyrotoxicosis; • Myelography.	**4.3 Contra indications**

4.4.1.3. Extravasation Extravasation is not an uncommon complication (0.04% to 0.9%) of intravenous injections of contrast media. More frequent with high-osmolarity contrast agents, most lesions are minor; however, severe lesions such as skin ulceration, tissue necrosis and compartment syndrome may occur with all iodinated contrast media. The factors of risk and/or seriousness are patient-related (poor vascular status or fragile patient) and technique-related (use of a pressure injector, large volume administered). It is important to identify these factors and optimise injection site and technique accordingly, and to monitor the patient before, during and after the injection of TELEBRIX 35.		
4.4.2. Precautions for use *4.4.2.1. 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 hypersensitivity reaction. 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. ▪ necessary resuscitation equipment at hand. • 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 – Undesirable effects).	***4.4.1.2. Precautions for use*** *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. 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).	**4.4 Special warnings and precautions for use**

4.4.2.2. Renal failure 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) recent myocardial infarction, intra-aortic balloon pump, low haematocrit, hyperuricaemia, or a history of renal failure following administration of iodinated contrast media, children under one year and atheromatous elderly subjects or with polymorbidity syndrome. • 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 angiotensin-converting enzyme (ACE) inhibitors, aminoglycosides, organoplatins, high-dose methotrexate, pentamidine, foscarnet and certain antivirals (aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, and tenofovir), vancomycin, amphotericin B, non-steroidal anti-inflammatory drugs, diuretics, immunosuppressants such as ciclosporine or tacrolimus, ifosfamide. • Since renal elimination is reduced in the presence of renal dysfunction, the interval between two X-ray examinations involving injection of an iodinated contrast medium must be as long as clinically acceptable, especially in risk patients. For these patients, allow for a 48- to 72-hour interval. In the event of renal failure following the first examination, any further examination should be deferred until after initial renal function has been restored. • Prevent lactic acidosis in diabetic patients treated with biguanides (metformin), according to creatinine clearance. (see 4.5. Interactions - Antidiabetic drugs belonging to the biguanides family). Haemodialysis patients may receive iodinated contrast media as these products are dialysable. The haemodialysis department must first be consulted.	*4.4.1.2.2. Renal failure* 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. Haemodialysis patients may receive iodinated contrast media as these products are dialysable. The haemodialysis department must first be consulted.	
4.4.2.5. 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. Their thyroid function should be therefore evaluated and monitored.	*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.	
4.4.2.11. Warnings concerning excipients This medicinal product contains 341.8 mg sodium per 100 mL. To be taken into consideration by patients on a controlled sodium diet.		
4.5.1. Medicinal products + **Antidiabetic drugs belonging to the biguanides family (metformin) (see section 4.4.2.2. Precautions for use - Renal failure)** 1. In patients with normal renal function, biguanide treatment can be continued normally.	**4.5.1. Medicinal products** • **Metformin in diabetics** (see section 4.4.2.2. Precautions for use – Renal Failure).	**4.5 Interaction with other medicinal products and other forms of Interaction**

2. In patients with moderate renal insufficiency (estimated Glomerular Filtration Rate (eGFR) 30-59 mL/min/1.73m²): Patients receiving intravenous contrast medium with eGFR equal to or greater than 45 mL/min/1.73 m² can continue to take the biguanide normally. Patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 mL/min/1.73 m², should stop the biguanide 48 h before contrast medium and should only restart the biguanide 48 hours after contrast medium if renal function has not deteriorated. 3. In patients with eGFR less than 30 mL/min/1.73 m² (Chronic Kidney Disease grade 4 and 5), or with an intercurrent illness causing reduced liver function or hypoxia, the biguanide is contraindicated and a careful risk/benefit assessment should precede the administration of any iodinated contrast media. 4. In emergency patients, the biguanide should be stopped from the time of contrast medium administration. After the procedure, the patient should be monitored for signs of lactic acidosis. The biguanide should be restarted 48 h after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level. + **Radiopharmaceuticals (see also 4.4.1.1. Special warnings)** A risk of hyperthyroidism or induction of hypothyroidism exists in at-risk patients. 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. Hypersensitivity reactions may be aggravated in patients taking beta-blockers, particularly in the presence of bronchial asthma. These patients may be refractory to standard treatment for hypersensitivity reactions with beta-agonists. The doctor must be informed if the patient is taking such treatment prior to injection of the iodinated contrast medium and have the necessary resuscitation means at hand.	• **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 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	

+ **Diuretics** Due to the risk of dehydration induced by diuretics, hydration is initially necessary for minimising the risk of acute renal failure. TELEBRIX 35 may have an additive diuretic effect because of its hyperosmolar properties. + **Interleukin 2** Enhanced reaction to contrast media during treatment with interleukin 2 (intravenous route) may occur: rash, congestive flush, erythema, fever or flu-like symptoms, or more rarely hypotension, oliguria or even renal failure. + **Potentially nephrotoxic agents (see section 4.4.2.2. Precautions for use - Renal failure)** + **Fibrinolytic agents** It has been demonstrated that, *in vitro*, contrast media perturb the effects of fibrinolytic agents in a dose-dependent manner. Given this enzyme inhibition, which varies between fibrinolytic agents, iodinated contrast media should not be administered concomitantly.	more rarely hypotension, oliguria or even kidney failure.	

Pregnancy Given that exposure to radiation should generally be avoided during pregnancy, whether a contrast agent is used or not, the benefit of a radiological examination must be carefully assessed.		
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. The thyroid function of neonates exposed in utero must be examined and monitored. 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.	**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.	**4.6 Pregnancy and lactation**
Since marketing, the most frequently reported undesirable effects after administration of all forms of TELEBRIX are: hypersensitivity (particularly anaphylactic reaction, anaphylactoid reaction and anaphylactic shock), urticaria, rash (particularly erythema and maculopapular rash) and reactions at injection site (such as oedema, pain and inflammation). Hypersensitivity reactions are usually immediate (occurring during administration or with the hour following the start of administration), but they may be delayed (from one hour to several days after administration), and are seen as undesirable cutaneous reactions. Immediate reactions may consist in one or several successive or concomitant effects, usually cutaneous reactions, respiratory and/or cardiovascular disorders, which may be the early signs of shock. They are rarely fatal. The undesirable effects given in the table below according to System Organ Class; frequency is unknown (cannot be estimated from available data). List summarising the undesirable effects with TELEBRIX 35 or another form of TELEBRIX after intravascular administration:	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% • 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 Undesirable effects**

System Organ Class	Frequency: undesirable effect
Immune system disorders	Unknown frequency: anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity
Endocrine disorders	Unknown frequency: thyrotoxic crisis*, hyperthyroidism*, thyroid disorder*
Psychiatric disorders	Unknown frequency: confusional state, agitation
Nervous system disorders	Unknown frequency: coma, syncope, convulsion, paresis/paralysis paresthesiae, tremor, headache
Cardiac disorders	Unknown frequency: cardiac arrest, myocardial infarction, angina pectoris, arrhythmia, tachycardia
Vascular disorders	Unknown frequency: hypotension, thrombophlebitis, circulatory collapse
Respiratory, thoracic and mediastinal disorders	Unknown frequency: respiratory arrest, laryngeal œdema, laryngospasm, pulmonary œdema, dyspnoea, bronchospasm, throat tightness, cough
Gastro-intestinal disorders	Unknown frequency: diarrhoea, nausea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Unknown frequency: *Immediate:* angiœdema, urticaria, pruritus, erythema *Delayed:* rash, rash maculo-papular
Renal and urinary disorders	Unknown frequency: renal failure acute, anuria
General disorders and administration site conditions	Unknown frequency: œdema, face œdema, pain, feeling hot, malaise, injection site extravasation, injection site pain, injection site inflammation, injection site oedema, injection site necrosis[1]
Investigations	Unknown frequency: Blood creatinine increased

[1] in the event of extravasation

* See section 4.4.1.2. Iodinated contrast media and the thyroid

The following undesirable effects have been reported with other iodinated contrast media or with TELEBRIX via a different route of administration.

Hence, they may occur during administration of TELEBRIX.

System Organ Class	Undesirable effect
Psychiatric disorders	Hallucinations, anxiety

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 35 (350 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 35 (350 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 35 (350 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

Nervous system disorders	Brain œdema, amnesia, dizziness, speech disorders, somnolence, dysgeusia
Eye disorders	Visual impairment, photophobia, blindness transient
Ear and labyrinth disorders	Hearing impaired
Cardiac disorders	Bradycardia
Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration[1], sneezing
Gastrointestinal disorders	Pancreatitis[2], ileus[3], parotid gland enlargement, salivary hypersecretion
Reproductive system and breast disorders	Pelvic pain[4]
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, eczema
Musculoskeletal and connective tissue disorders	Arthralgia[5]
Investigations	Electroencephalogram abnormal, blood amylase increased

[1] in patients with swallowing disorders (oral route)

[2] after endoscopic retrograde cholangio-pancreatography (ERCP)

[3] after enteral administration

[4] in the event of hysterosalpingography

[5] in the event of arthrography

Undesirable effects in children

The known nature of undesirable effects associated with TELEBRIX 35 is the same as that of effects reported in adults. Their frequency cannot be estimated from available data.

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 found at high levels in the cerebral arterial blood: agitation, confusional state, tremor, paresthesiae, paresis/paralysis, convulsion, coma.

Not reported with TELEBRIX 35 (350 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 35 (350 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 35 (350 mg I/mL), solution for injection: joint pain in the event of arthrography.	
Overdose increases the risk of kidney disease and may cause 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**

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.
שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך 6/2013

☒ כל השינויים עולים בקנה אחד עם תנאי הרישום (תעודת הרישום, תעודת האיכות וטופס פרטי התכשיר העדכני).
☒ כל הכתוב בהצעת העלון, תואם את תנאי הרישום.
☐ קיים עלון לצרכן והוא מעודכן בהתאם. – קיים רק עלון לרופא
☒ אסמכתא לבקשה: עלון לרופא מאושר בצרפת.
האסמכתא מצ"ב.
☒ השינוי הנ"ל אושר על ידי רשויות הבריאות בצרפת

☒ אני, הרוקח הממונה של חברת פרומדיקו בע"מ מצהיר בזה כי אין שינויים נוספים , מלבד אלה שסומנו בהצעת העלון.
☒ אני מצהיר כי השינויים אינם יוצרים סתירה פנימית במידע בעלון.

עלון זה לא מטופל במקביל במסגרת אחרת (כגון: עדכון עלון במסגרת בקשה לתוספת התוויה, החמרה וכו') . במידה וקיים טיפול מקביל במסגרת אחרת- יש לציין זאת.

חתימת הרוקח הממונה (שם וחתימה)_____