SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TELEBRIX 30 MEGLUMINE (300 mg Iodine/mL), solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For 100 mL of solution:

Meglumine ioxitalamate…….....66.03 g

Equivalent to iodine……. .....30 g

- Iodine content per mL: 300 mg
- Iodine mass per 30 mL vial: 9 g
- Iodine mass per 50 mL vial: 15 g
- Iodine mass per 100 mL bottle: 30 g

Excipient with known effect: Sodium (8.4 mg sodium per 100 mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

- Viscosity at 20° C: 10.2 mPa.s
- Viscosity at 37° C: 5.3 mPa.s
- Osmolality: 1710 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Contrast medium for use in adults and children-via intra -arterial and intravenous administration and by instillation for:
Urograph, selective angiography, peripheral angiography, arthrography, hysterosalpingography and digestive exploration.

4.2. Posology and method of administration

Posology

The dose must be adapted according to the patient's age, weight , renal function, the type of examination and the volume of the organ to be examined.

Indications	Average dose mL/kg	Total volume (min.-max.) mL
Intravenous urography	The standard dose is 1 to 2 ml/kg. In children under 20 kg, the dose is 2 to 3 ml/kg.	50 – 100 mL
Retrograde urethrocystography	Dosage to be adapted to the volume of the organ to be injected.	20 – 100 mL
Suprapubic cystography	Dosage to be adapted to the volume of the organ to be injected.	100 – 250 mL

Special populations

Elderly patients

TELEBRIX 30 Meglumine should be administered with caution (see section 4.4), in well-hydrated patients at the minimum effective dose.

Paediatric population

As with all other hyperosmolar contrast media, the use of this preparation should be carefully considered in neonates, infants, and children. The administered dose should be reduced to the minimum.

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 and intravenous injection, or by instillation.

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 30 Meglumine (300 mg Iodine/mL), solution for injection;
- Decompensated heart failure;
- Manifest thyrotoxicosis;
- Intrathecal or subarachnoid (or epidural) administration of TELEBRIX 30 Meglumine 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

- Allergic reaction is possible regardless of the administration route and dose.
- The intolerance risk is not univocal in the case of medicinal products administered locally for opacification of bodily cavities:

a) Administration by certain specific routes (articular, biliary, intrathecal, intrauterine, etc.) leads to considerable systemic passage: systemic effects may therefore be observed.

b) Administration by oral or rectal route generally leads to very limited systemic diffusion; if the gastro-intestinal mucosa is normal, only 5% maximum of the dose administered is found in the urine, the remainder being eliminated in the faeces. However, if the gastro-intestinal mucosa is altered, absorption is increased; it becomes total and rapid in the event of perforation, with passage into the cavity of the peritoneum. The medicinal product is then eliminated in the urine. The occurrence of any dose-dependent systemic effects therefore depends on the condition of the gastro-intestinal mucosa.

c) The immuno-allergic mechanism is however not dose-dependent and always likely to be observed, regardless of the administration route.

With respect to the prevalence and the intensity of adverse effects, the following therefore are antagonists:

- Medicinal products administered by vascular route and by certain local routes
- Medicinal products administered by intestinal route and little absorbed under normal conditions

4.4.1. Special warnings

4.4.1.1. Hypersensitivity

Any 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-type allergy dependent on the contrast medium (anaphylaxis)
- Cell-mediated allergic reactions (late onset cutaneous 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 4.4.2.5. Precautions for use - Dysthyroidism)

Prior to administration of an iodinated contrast medium, it must be ensured that the patient is not to undergo a scintigraphic exploration of the thyroid, or administration of radioactive iodine treatment.

Administration of iodinated contrast media, regardless of the route, disturbs hormone assays and iodine fixation by the thyroid or thyroid cancer metastases until normalisation of urine iodine levels.

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 30 Meglumine.

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).

4.4.2.2 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.

4.4.2.3. 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.

4.4.2.4. 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.

4.4.2.5. 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.

4.4.2.6. 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.

4.4.2.7. 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.

4.4.2.8. Pheochromocytoma

Patients suffering from phaechromocytoma may experience hypertension surge following intravascular administration of a contrast medium and may require appropriate treatment prior to the procedure.

4.4.2.9. Myasthenia

Administration of a contrast medium may worsen myasthenia symptoms.

4.4.2.10. 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.

4.4.2.11. Warnings about excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mL, so it is practically sodium-free.

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

4.5.1. Medicinal products

+ **Antidiabetic in the biguanides group (metformin) (see also section 4.4.2.2. Precautions for use - Renal failure)**

1. In patients with normal renal function, biguanide treatment can be continued normally.

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 section 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 dispose of the necessary resuscitation means.

+ **Diuretics**

Due to the risk of dehydration induced by diuretics, hydration is initially necessary for minimising the risk of acute renal failure.

TELEBRIX 30 Meglumine 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.

4.5.2. Other forms of interaction

High concentrations of iodinated contrast media in plasma and urine may interfere with *in vitro* bilirubin, protein and inorganic substance assay (iron, copper, calcium and phosphate); it is therefore recommended to not perform assay of these substances during the 24 hours following the procedure.

4.6 Pregnancy and lactation

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.

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. 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.

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.

4.7. Effects on ability to drive and use machines

No study on the effect on the ability to drive and use machines has been conducted.

Given the pharmacological properties of TELEBRIX 30 Meglumine itself, any effect on the ability to drive and use machines is unlikely.

4.8. Undesirable effects

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 the injection site (such as oedema, pain and inflammation).

Hypersensitivity reactions are usually immediate (occurring during administration or within 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 are presented in the table below according to System Organ Class; frequency is unknown (cannot be estimated from the available data).

List summarising the undesirable effects reported with TELEBRIX 30 Meglumine or another form of TELEBRIX after intravascular administration or instillation:

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, dizziness, 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, bronchospasm, throat tightness, cough
Gastrointestinal disorders	Unknown frequency: diarrhoea, nausea, vomiting, abdominal pain
Skin and subcutaneous tissue disorders	Unknown frequency: *Immediate:* angiœdema, urticaria, pruritus, erythema *Delayed:*rash maculo-papular
Renal and urinary disorders	Unknown frequency: renal failure acute, anuria
General disorders and administration site conditions	Unknown frequency: œdema, face oedema, 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
Nervous system disorders	Brain œdema, amnesia, speech disorder, 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,

System Organ Class	Undesirable effect
	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 30 Meglumine is the same as that of effects reported in adults. Their frequency cannot be estimated from available data.

4.9. Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

TELEBRIX 30 MEGLUMINE (300 mg Iodine/mL), solution for injection is an ionic, nephrotropic, water soluble uro-angiographic contrast medium with an osmolality of 1710 mOsm/kg.

5.2. Pharmacokinetic properties

Injected by vascular route, ioxitalamic acid is distributed to the intravascular compartment and the interstitial space. The elimination half life is 1.1 hour, the distribution volume 194 mL/kg and total clearance 120 mL/min on average. It is mainly eliminated by renal route (glomerular filtration without re-absorption or tubular secretion) in unchanged form. The osmotic diuresis effect induced by TELEBRIX 30 MEGLUMINE is related to the osmolality and volume of the medium injected.

In the event of renal failure, heterotropic renal elimination takes place by biliary, salivary, sudoral and colic route. The substance is dialysable.

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

Meglumine, sodium calcium edetate, sodium dihydrogen phosphate dihydrate, water for injections.

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 25°C.
Keep protected from light.

6.5. Nature and contents of container

30 mL, 50 mL and 100 mL colourless glass vials/bottles (type II) with an elastomer stoppers (chlorobutyl).

Not all pack sizes may be marketed.

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

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FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

027-67-21780-00

9. REGISTRATION HOLDER

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10. DATE OF APPROVAL/REVISION

The format of this leaflet has been defined by the MOH and its content has been checked and approved, June 2013