

SUMMARY OF PRODUCT CHARACTERISTICS

1. **NAME OF THE MEDICINAL PRODUCT**

Thallium (^{201}Tl) chloride CIS bio international 37 MBq/mL solution for injection
Reference: TL-201-S-1

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 mL of solution contains 37 MBq of thallos chloride (^{201}Tl) at calibration date.

The activity per vial varies from 37 MBq to 555 MBq at calibration date.

Thallium (^{201}Tl) decays to mercury (^{201}Hg) by electron capture with a half-life of 3.04 ± 0.04 days. The most prominent gamma photons of thallium-201 have energies of 167 keV (10 %) and 135 keV (2.6 %). The X-rays have energies of 69 keV to 71 keV (73.7 %).

Excipient with known effect: sodium (3.3 mg/mL)
For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection.
Clear and colourless solution with a pH ranging between 4.0 and 7.0.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

This medicinal product is for diagnostic use only.

Thallium (^{201}Tl) chloride CIS bio international is indicated in adults for:

- Myocardial scintigraphy in the evaluation of coronary perfusion and cellular viability: ischemic heart disease, cardiomyopathies, myocarditis, myocardial contusions and secondary cardiac lesions.
- Scintigraphy of the muscles: muscle perfusion in peripheral vascular disorders.
- Parathyroid scintigraphy.
- Thallium-avid tumour visualisation in different organs, especially for the brain tumours and thyroid tumours and metastases.

4.2. Posology and method of administration

This medicinal product is for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel.

Posology

Adults and elderly population

Injection of 0.74 to 1.11 MBq/kg of thallium (^{201}Tl) chloride solution. This activity can be increased by fifty percent until a maximum activity of 110 MBq, if SPECT-imaging is considered.

Method of administration

This medicinal product is for intravenous use only.

For myocardial scintigraphy, thallium (^{201}Tl) chloride injection can be done either at rest or during intervention tests: conventional stress test or a similar test like electrostimulation or pharmacological test.

Image acquisition

a) Myocardial scintigraphy:

The first set of images during stress test can be acquired few minutes after injection.

Thallium redistribution can be studied with a new set of images acquisition obtained between 3 to 24 hours after injection.

In some cases, instead of the redistribution study (or after it), reinjection of 37 MBq of thallium can be done to evaluate myocardium viability. Acquisition of images starts 10 minutes after injection.

b) Non-myocardial indications:

Image acquisitions can be started during/or few minutes after injection ("Flow images") and/or later ("cell uptake images").

For patient preparation, see section 4.4.

4.3. Contra-indications

- Hypersensitivity to the active substance, to any of the excipients listed in section 6.1.
- Pregnancy.
- Breastfeeding.
- Children below the age of 18 years. In young children $^{99\text{m}}\text{Tc}$ labelled myocardial perfusion agents must be used because of their lower radiation burden.
- Specific contra-indications of associated interventional, when a stress test or stimulation is planned.

4.4. Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

It is usually not possible to differentiate recent from old myocardial infarction, or to differentiate exactly between recent myocardial infarction and ischemia.

Patient preparation

For myocardial scintigraphy, fasting during 4 hours before the examination is recommended.

The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the study in order to reduce radiation.

Strict cardiological monitoring and the material required for emergency treatment are essential when performing interventional tests: exercise or pharmacological stimulation.

The insertion of a flexible indwelling catheter is recommended during the entire examination.

Paravenous injection must be avoided due to the risk of local tissue necrosis. Injection should be strictly intravenous to avoid thallium (^{201}Tl) chloride local deposit and irradiation. In the event of paravenous injection, the injection should be immediately stopped and the site of injection should be cooled and rested in elevated position. When radiation necrosis occurs, surgical intervention may be necessary.

Specific warnings

This medicinal product contains less than 1 mmol of sodium (23 mg) per dose, i.e. essentially "sodium free".

Precautions with respect to environmental hazard, see section 6.6.

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

Some drugs are responsible for interferences modifying the thallium (^{201}Tl) myocardial uptake.

Three processes could be implied:

- Direct or indirect variations of the coronary blood flow (dipyridamole, adenosine, isoprenaline, dobutamine, nitrates ...);
- Interferences with the interventional tests (beta blockers and stress tests, methylxanthines (i.e. theophyllin) and dipyridamole...);
- Thallium cell uptake modifications, although no definitive data are available (digitalis analogues, insulin have been mentioned as examples).

Digitalis glycosides, betablockers and methylxanthines like theophylline lead to decreased uptake of thallium (^{201}Tl) to the myocard. Nitrates, dipyridamole, insulin, atropine and calcium lead to increased uptake of thallium (^{201}Tl).

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

No data are available on the use of thallium (^{201}Tl) chloride in pregnancy. According to the high uterus radiation doses, thallium (^{201}Tl) chloride injection is contraindicated during pregnancy (see section 4.3).

Breastfeeding

Thallium (^{201}Tl) chloride injection is contraindicated in breastfeeding mothers.

Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of the radionuclide until the mother has ceased breastfeeding and to what is the most appropriate choice of radiopharmaceutical, bearing in mind the lack of data concerning the secretion of thallium (^{201}Tl) in the milk. If the administration is considered necessary, breastfeeding should be discontinued and the expressed feeds discarded.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Information on adverse reactions is available from spontaneous reporting. The reports describe anaphylactoid, vasovagal and injection site reactions which were mild to moderate and usually resolved with either no or symptomatic treatment.

The undesirable effects are classified in accordance with the MedDRA System Organ Class, with an unknown frequency (cannot be estimated from the available data).

Injury, poisoning and procedural complications:

Frequency unknown: Local radiation necrosis after paravenous injection.

For myocardial scintigraphy, the cardiac stress is induced by ergometric exercise or by the use of appropriate medication. A patient may experience adverse reactions as a result of cardiac stress. Depending on the method used for inducing stress, such reactions include cardiovascular symptoms like palpitations, ECG abnormalities, arrhythmia, chest pain, shortness of breath, and ultimately myocardial infarction. Other symptoms related to the induced stress are hypertension or hypotension, chills, dysgeusia, nausea, vomiting and general fatigue or malaise.

Immune system disorders:

Frequency unknown: Anaphylactic reactions (e.g. laryngospasm, pharyngitis, laryngea oedema, dyspnoea, rash pustular, rash erythematous, hypersensitivity, pain of skin, facial pain, tongue oedema, face oedema, oedema, conjunctivitis, lacrimal disorder, erythema, pruritus, rash, urticaria, flushing, hyperhidrosis, cough).

Nervous system disorders:

Frequency unknown: Presyncope (e.g. syncope, dizziness, bradycardia, hypotension, tremor, headache, pallor).

General disorders and administration site conditions

Frequency unknown: Injection site reaction.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

As the effective dose is 15.4 mSv when the maximal recommended activity of 110 MBq is administered these adverse events are expected to occur with a low probability.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

The risk of overdose lies in an unintentional high exposure to ionising radiation. In the event of the administration of a radiation overdose with thallium (^{201}Tl) chloride the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis with frequent voiding and stimulation of the gastro-intestinal passage. Gastro-intestinal absorption of thallium (^{201}Tl) chloride may be prevented by administration of the antidote ferric hexacyanoferrate(II).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: **Radiopharmaceutical product for diagnostic use.**

ATC code: **V09GX01**

At the chemical concentrations used for diagnostic procedures, thallium (^{201}Tl) chloride does not appear to have any pharmacodynamic activity.

5.2. Pharmacokinetic properties

Distribution

After intravenous injection of thallium (^{201}Tl) chloride, the thallium rapidly leaves the blood as approximately 90 % is cleared after the first pass.

Organ uptake

The relative uptake depends on regional perfusion and on the cell extraction efficacy of different organs. The myocardial extraction fraction of thallium (^{201}Tl) is about 85 % during the first pass and the peak myocardial activity is 4-5 % of the injected dose, relatively constant for about 20-25 minutes. The precise cellular uptake process is still questioned but the sodium-potassium ATPase pump is probably involved, at least in part. The muscular uptake is dependent on workload and compared with the resting condition, the uptake in skeletal muscle and myocardium is increased 2-3 fold during exercise with consequently reduction in other organs.

Elimination

Thallium is mainly excreted in the faeces (80 %) and in the urine (20 %).

Half-life

The effective half-life is about 60 hours and its biological half-life about 10 days.

5.3. Preclinical safety data

Thallium is one of the most toxic chemical elements with a lethal dose in man of about 500 mg. Toxicological studies in animals with thallosal salts using intravenous administration show lethal doses ranging from 8 to 45 mg/kg of body weight. The doses used in man for scintigraphy are ten thousand times smaller than these toxic doses. Studies in the mouse and the rat demonstrated considerable transplacental passage of thallium.

This medicinal product is not intended for regular or continuous administration.

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Sodium chloride
- 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

14 days from the manufacturing date

After the first withdrawal, store the product in a refrigerator (2°C and 8°C) and use within the day.

6.4. Special precautions for storage

Do not store above 25°C. Store in its original packaging.

For storage conditions after first withdrawal, see section 6.3.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5. Nature and contents of container

15 ml, colourless, European Pharmacopoeia type I, drawn glass vial, closed with chlorobutyl rubber stopper and aluminium capsule.

Pack size: 1 multidose vial containing 1 to 15 mL, corresponding to 37 to 555 MBq at calibration date.

6.6. Special precautions for disposal and other handling

General warning

Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

If the integrity of this vial is compromised, the product should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The vial must be kept inside its lead shielding.

The vial must not be opened. After disinfection of the stopper, the solution should be withdrawn through the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7. MARKETING AUTHORISATION HOLDER

Country specific

8. MARKETING AUTHORISATION NUMBER

Country specific

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Country specific

10. DATE OF REVISION OF THE TEXT

11/2013

11. DOSIMETRY

According to Publication 106 of the ICRP (International Commission on Radiological Protection), doses of radiation absorbed by patients are as follows:

Absorbed dose per unit activity administered (resting subject) (mGy/MBq)

Organ	Adult
Adrenals	0.057
Bladder	0.039
Bone surfaces	0.38
Brain	0.022
Breast	0.024
Gall bladder	0.065
GI-tract	
Stomach	0.11
Small Intestine	0.14
Colon	0.25
ULI	0.18
LLI	0.34
Heart	0.19
Kidneys	0.48
Liver	0.15
Lungs	0.11
Muscles	0.052
Oesophagus	0.036
Ovaries	0.12
Pancreas	0.057
Red marrow	0.11
Skin	0.021
Spleen	0.12
Testes	0.18
Thymus	0.036
Thyroid	0.22
Uterus	0.050
Remaining organs	0.054
Effective dose (mSv/MBq)	0.14

For thallium (^{201}Tl) chloride, the effective dose resulting from an administered activity of 110 MBq is typically 15.4 mSv (per 70 kg individual).

For this administered activity of 110 MBq, the typical radiation dose to the target organ (myocardium) is 20.9 mGy and the typical radiation doses to the critical organs (kidneys and lower large intestine) are 52.8 mGy and 37.4 mGy respectively.

According to Publication 53 of the ICRP (International Commission on Radiological Protection):

**Effective dose equivalent in relation to impurities
(mSv/MBq of impurity)**

^{200}Tl (26.1 h)	0.31
^{202}Tl (12.23 d)	0.81