SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Thallium [201Tl] chloride injection, CIS bio international
Reference: TL-201-S-1

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Thallium [201Tl] chloride injection is a sterile isotonic solution with a pH ranging between 4.0 and 7.0. The specific radioactivity is greater than or equal to 3.7 MBq/µg (0.1 mCi/µg) of thallium. The radioactive concentration is 37 MBq/mL (1 mCi/mL) at the reference date stated on the label (calibration date). The radiochemical purity is at least equal to 95 %.

Composition of the medicinal product:

- Active ingredient:
  Thallium [201Tl] chloride : 37 MBq/mL (at calibration date)

- Other ingredients:
  Sodium chloride : up to isotonicity
  Water for injections : up to 1 ml

Thallium [201Tl] (atomic number: 81, atomic weight: 201) decays to mercury [201Hg] by electron capture with a half-life of 3.0408 ± 0.0420 days. Not less than 97.0 % of the total radioactivity is due to thallium [201Tl]. At the calibration date, not more than 0.25 % of the total radioactivity is due to thallium [200Tl], not more than 0.50 % is due to thallium [202Tl] and not more than 0.10 % is due to lead [203Pb].

Radiation characteristics of thallium [201Tl]:

<table>
<thead>
<tr>
<th>TYPE OF RADIATION</th>
<th>ENERGY (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>69&lt;br&gt;83</td>
</tr>
<tr>
<td>γ</td>
<td>135&lt;br&gt;166&lt;br&gt;167</td>
</tr>
</tbody>
</table>
Thallium $^{201}$Tl decay chart:

<table>
<thead>
<tr>
<th>Days</th>
<th>Decay factor</th>
<th>Days</th>
<th>Decay factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 5</td>
<td>3.13</td>
<td>1.5</td>
<td>0.71</td>
</tr>
<tr>
<td>- 4.5</td>
<td>2.79</td>
<td>2</td>
<td>0.63</td>
</tr>
<tr>
<td>- 4</td>
<td>2.49</td>
<td>2.5</td>
<td>0.57</td>
</tr>
<tr>
<td>- 3.5</td>
<td>2.22</td>
<td>3</td>
<td>0.50</td>
</tr>
<tr>
<td>- 3</td>
<td>1.98</td>
<td>3.5</td>
<td>0.45</td>
</tr>
<tr>
<td>- 2.5</td>
<td>1.77</td>
<td>4</td>
<td>0.40</td>
</tr>
<tr>
<td>- 2</td>
<td>1.58</td>
<td>4.5</td>
<td>0.36</td>
</tr>
<tr>
<td>- 1.5</td>
<td>1.41</td>
<td>5</td>
<td>0.32</td>
</tr>
<tr>
<td>- 1</td>
<td>1.26</td>
<td>5.5</td>
<td>0.29</td>
</tr>
<tr>
<td>- 0.5</td>
<td>1.12</td>
<td>6</td>
<td>0.25</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>6.5</td>
<td>0.23</td>
</tr>
<tr>
<td>0.5</td>
<td>0.89</td>
<td>7</td>
<td>0.20</td>
</tr>
<tr>
<td>1</td>
<td>0.80</td>
<td>7.5</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>0.16</td>
</tr>
</tbody>
</table>

3. PHARMACEUTICAL FORM

Solution for injections.

4. CLINICAL PARTICULARS

4.1. Diagnostic indications

- Myocardial scintigraphy in the evaluation of coronary perfusion and cellular viability: ischaemic 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

Injection of 0.74 to 1.11 MBq/kg (0.02 to 0.03 mCi/kg) in adults and the elderly of thallium $^{201}$Tl chloride solution via the intravenous route. This activity can be increased by fifty percent if SPECT-imaging is considered until a maximum activity of 110 MBq (3 mCi).

a) Myocardial scintigraphy:

Fasting during 4 hours before the examination is recommended.

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.

The first set of images 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 (1 mCi) of thallium can be done to evaluate myocardium viability.

b) Non-myocardial indications:

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

4.3. Contra-indications

- Hypersensitivity to Thallium $^{201}$Tl chloride injection.
- Thallium $^{201}$Tl chloride injection must not be administered to pregnant women and breast feeding mothers as well as to children and adolescents.
- The specific contra-indications of associated interventional tests should be considered.

4.4. Special warnings and special precautions for use

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.

Patient preparation
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. The insertion of a flexible in-dwelling catheter is recommended during the entire examination.

Strict cardiological monitoring and the material required for emergency treatment are essential when performing interventional tests (exercise, pharmacological, electrical. It is usually not possible to differentiate recent from old myocardial infarction, or to differentiate exactly between recent myocardial infarction and ischemia.

If anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and, if necessary, intravenous treatment initiated. Respective medicinal products and equipment (e.g. endotracheal tube and ventilator) have to be readily available.
Paravenous injection must be avoided due to the risk of local tissue necrosis. Injection should be strictly intravenous to avoid thallium \(^{201}\text{TI}\) 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.

General warnings
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 licences of the competent official organisation. Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

4.5. Interaction with other medicaments and other forms of interaction

Some drugs are responsible for interferences modifying the thallium \(^{201}\text{TI}\) 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).

4.6. Pregnancy and lactation

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

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.

Breastfeeding
Thallous \(^{201}\text{TI}\) chloride injection is contraindicated in breast-feeding mothers. Before administering radiopharmaceutical to a mother who is breast-feeding consideration should be given as to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding and to what is the most appropriate choice of radiopharmaceutical, bearing in mind the lack of data concerning the secretion of thallium \(^{201}\text{TI}\) in the milk. If the administration is considered necessary, breast feeding should be discontinued.

4.7. Effects on ability to drive and use machines

Effects on ability to drive vehicles or to operate machines have not been described.
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. Local radiation
necrosis has been reported after paravenous injection.

Adverse Reactions sorted by System Organ Class:

Immune system disorders
Frequency unknown*: Anaphylactic reactions (e.g. laryngospasm, pharyngitis, laryngeal
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, hyperhydrosis, cough)

Nervous system disorders
Frequency unknown*: Vasovagal reactions (e.g. syncope, dizziness, bradycardia, hypotension,
tremor, headache, pallor)

General disorders and administration site conditions
Frequency unknown*: Injection site reaction

Injury, poisoning and procedural complications
Frequency unknown*: Local radiation necrosis after paravenous injection.

* Adverse reactions derived from spontaneous reporting

Thallium $^{201}$Tl chloride is often used in combination with a cardiac stress-test. The
cardiac stress is hereby 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.

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.

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 thallous $^{201}$Tl
chloride may be prevented by administration of the antidote ferric hexacyanoferrate(II).
5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

At the chemical concentrations and activities used for diagnostic procedures, thallium \([^{201}\text{Tl}]\) chloride does not appear to exert any pharmacodynamic effects.

5.2. Pharmacokinetic properties

After intravenous injection of thallium \([^{201}\text{Tl}]\) chloride, the thallium rapidly leaves the blood as approximately 90 % is cleared after the first pass. The relative uptake depends on regional perfusion and on the cell extraction efficacy of different organs. The myocardial extraction fraction of thallium \([^{201}\text{Tl}]\) 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.

Thallium is mainly excreted in the faeces (80 %) and in the urine (20 %). 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 thallous 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.
5.4. Radiation dosimetry

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

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>ABSORBED DOSE PER UNIT ACTIVITY ADMINISTERED (RESTING SUBJECT) (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.057</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>0.039</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.38</td>
</tr>
<tr>
<td>Brain</td>
<td>0.022</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.024</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>0.065</td>
</tr>
<tr>
<td>Gastronintestinal tract</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>0.11</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.14</td>
</tr>
<tr>
<td>Colon</td>
<td>0.25</td>
</tr>
<tr>
<td>Upper Large Intestine</td>
<td>0.18</td>
</tr>
<tr>
<td>Lower Large Intestine</td>
<td>0.34</td>
</tr>
<tr>
<td>Heart</td>
<td>0.19</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.48</td>
</tr>
<tr>
<td>Liver</td>
<td>0.15</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.11</td>
</tr>
<tr>
<td>Muscles</td>
<td>0.052</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>0.036</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.12</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.057</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.11</td>
</tr>
<tr>
<td>Skin</td>
<td>0.021</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.12</td>
</tr>
<tr>
<td>Testes</td>
<td>0.18</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.036</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.22</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.050</td>
</tr>
<tr>
<td>Remaining organs</td>
<td>0.054</td>
</tr>
<tr>
<td>Effective dose (mSv/MBq)</td>
<td>0.14</td>
</tr>
</tbody>
</table>
For thallium $^{201}$TI 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 (2.1 mCi), 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):

<table>
<thead>
<tr>
<th>EFFECTIVE DOSE EQUIVALENT IN RELATION TO IMPURITIES (mSv/MBq of impurity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{201}$TI (26.1 h)</td>
</tr>
<tr>
<td>$^{202}$TI (12.23 d)</td>
</tr>
</tbody>
</table>

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
   - Sodium chloride
   - Water for injections

6.2. Incompatibilities

None known.

6.3. Shelf life

The expiry date for this product is 14 days from the manufacturing date. The expiry date is indicated on the outer packaging of each vial.

6.4. Special precautions for storage

This product should be stored at a temperature ranging between +15 °C and +25 °C in its original packaging.

Storage should take place in accordance with national regulations for radioactive materials.

6.5. Nature and contents of container

15 mL, colourless, European Pharmacopoeia type I, drawn glass vial, closed with rubber stopper and aluminium capsule.
6.6. **Instructions for use / handling**

Usual precautions regarding sterility and radiation safety should be respected.

The vial must be kept inside its lead shielding.

Before use, packaging, pH, radioactivity and gamma spectrum will be checked.

The vial should never be opened. After desinfection of the stopper, the solution should be withdrawn aseptically through the stopper using single use sterile needle and syringe.

After first withdrawing, the remaining thallium $^{201}$Tl chloride injection should be kept at a temperature ranging between +2 °C and +8 °C and should be used within 24 hours.

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

The disposal of radioactive waste should be in accordance with relevant national and international regulations.

7. **MARKETING AUTHORISATION HOLDER**

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FRANCE  
Tel. : +33-(0)1.69.85.70.70  
Fax : +33-(0)1.69.85.70.71

8. **MARKETING AUTHORISATION NUMBER**

PL/11876/0012

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

03 October 1996

10. **DATE OF (PARTIAL) REVISION OF THE TEXT**

13/01/2016