

THALLIUM [²⁰¹Tl] CHLORIDE INJECTION

TL-201-S-1

TECHNICAL LEAFLET: 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 an 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] :

TYPE OF RADIATION	ENERGY (keV)
X	69
	83
γ	135
	166
	167

Thallium [²⁰¹Tl] decay chart :

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

3. **PHARMACEUTICAL FORM**

Solution for injections.

4. **CLINICAL PARTICULARS**

4.1. **Diagnostic indications**

- 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**

Injection of 0.74 to 1.11 MBq/kg (0.02 to 0.03 mCi/kg) in adults and the elderly of thallium [²⁰¹Tl] 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).

The activity to be administered to a child should be a fraction of the adult activity calculated from the body weight according to the following table.

3 kg = 0.1	22 kg = 0.50	42 kg = 0.78
4 kg = 0.14	24 kg = 0.53	44 kg = 0.80
6 kg = 0.19	26 kg = 0.56	46 kg = 0.82
8 kg = 0.23	28 kg = 0.58	48 kg = 0.85
10 kg = 0.27	30 kg = 0.62	50 kg = 0.88
12 kg = 0.32	32 kg = 0.65	52-54 kg = 0.90
14 kg = 0.36	34 kg = 0.68	56-58 kg = 0.92
16 kg = 0.40	36 kg = 0.71	60-62 kg = 0.96
18 kg = 0.44	38 kg = 0.73	64-66 kg = 0.98
20 kg = 0.46	40 kg = 0.76	68 kg = 0.99

In very young children (under 1 month) a minimum dose of 18.5 MBq (0.5 mCi) is necessary in order to obtain images of sufficient quality.

a) Myocardial scintigraphy :

Fasting during 4 hours before the examination is recommended.

Thallium [²⁰¹Tl] 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

- Thallium [²⁰¹Tl] chloride injection must not be administered to pregnant women and breast feeding mothers.
- The specific contra-indications of associated interventional tests should be considered.

4.4. Special warnings and special precautions for use

In young children the use of ^{99m}Tc labelled myocardial perfusion agents should be preferred because of their lower radiation burden.

Strict cardiological monitoring and the material required for emergency treatment are essential when performing interventional tests (exercise, pharmacological, electrical).

Injection should be strictly intravenous to avoid thallium [^{201}Tl] chloride local deposit and irradiation.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations.

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, complying with the requirements of Good Manufacturing Practices for pharmaceuticals.

4.5. Interaction with other medicaments 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).

4.6. Pregnancy and lactation

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.

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

Before administering a radioactive medicinal product to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the lack of data concerning the secretion of thallium [^{201}Tl] 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

- Rare allergic reactions and vasovagal effects have been reported without more precise information about the frequency of these effects.
- Local radiation necrosis has been reported after paravenous injection.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with a low frequency because of the low radiation doses incurred.

For most diagnostic investigations using a nuclear procedure the radiation dose delivered (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9. Overdose

In the event of the administration of a radiation overdose with thallium [²⁰¹Tl] 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

At the chemical concentrations and activities used for diagnostic procedures, thallium [²⁰¹Tl] chloride does not appear to exert any pharmacodynamic effects.

5.2. Pharmacokinetic properties

After intravenous injection of thallium [²⁰¹Tl] 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 [²⁰¹Tl] 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 thallos 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

For thallium [^{201}Tl] chloride, the effective dose equivalent resulting from an administered activity of 78 MBq (2.1 mCi) is typically 18 mSv (per 70 kg individual). For this administered activity of 78 MBq (2.1 mCi), the typical radiation dose to the target organ (myocardium) is 18 mGy and the typical radiation doses to the critical organs (kidneys and descending colon) are 42 mGy and 28 mGy respectively.

ORGAN	ABSORBED DOSE (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	0.051	0.066	0.099	0.14	0.25
Bladder wall	0.036	0.048	0.071	0.10	0.20
Bone surface	0.34	0.45	0.73	1.3	2.9
Chest	0.028	0.025	0.041	0.064	0.12
Stomach	0.12	0.16	0.24	0.40	0.78
Small intestine	0.16	0.21	0.36	0.57	1.1
Ascending colon	0.19	0.23	0.40	0.65	1.2
Descending colon	0.36	0.45	0.78	1.3	2.5
Heart	0.23	0.25	0.39	1.2	2.1
Kidneys	0.54	0.66	0.94	1.4	2.5
Liver	0.18	0.22	0.34	0.51	0.96
Lungs	0.12	0.18	0.26	0.41	0.79
Ovaries	0.12	0.13	0.32	0.54	1.2
Pancreas	0.054	0.065	0.10	0.15	0.26
Bone marrow	0.18	0.24	0.39	0.69	1.4
Spleen	0.14	0.19	0.29	0.46	0.83
Testes	0.56	1.2	9.7	11	15
Thyroid	0.25	0.40	0.62	1.4	2.7
Uterus	0.050	0.056	0.091	0.13	0.24
Other tissues	0.056	0.057	0.091	0.15	0.28
	EFFECTIVE DOSE EQUIVALENT (mSv/MBq)				
	0.23	0.36	1.5	2.0	3.0
	EFFECTIVE DOSE EQUIVALENT IN RELATION TO IMPURITIES (mSv/MBq of impurity)				
^{200}Tl (26.1 h)	0.31	0.47	1.2	1.5	2.3
^{202}Tl (12.23 d)	0.81	1.1	3.1	4.2	6.5

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 [²⁰¹Tl] 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

CIS bio international
B.P. 32
91192 Gif-sur-Yvette Cedex
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

04/2006