SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Thallous (Tl201) chloride injection 37MBq/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tl201-Thallium as thallous chloride 37 MBq/ml
The specific activity is more than 18.5 GBq /mg thallium. Tl201 decays to Hg201 by electron capture with a half-life of 73.1 hours.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

- 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

Posology
Adults and elderly

- Injection of 0.74 to 1.11 MBq/kg in adults and the elderly of thallous (Tl201) chloride solution via the intravenous route. This activity can be increased by 50 % if SPECT-imaging is considered until a maximum activity of 110 MBq.

Method of administration
For multi-dose use.
Administration is by intravenous injection.
For instructions for preparation of the medicinal product, see section 12.
For patient preparation, see section 4.4.

Image acquisition

Myocardial Scintigraphy:
Fasting during 4 hours before the examination is recommended.
Thallous chloride (Tl201) 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), reinduction of 37 MBq of thallium can be done to evaluate myocardium viability.

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

4.3 Contraindications

- Hypersensitivity to thallous (Tl201) chloride or to any of the excipients.
- Thallous (Tl201) chloride injection must not be administered to pregnant women and breast-feeding mothers as well as to children and adolescents.
- The specific contraindications of associated interventional tests should be considered.

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.

Paediatric population
In young children the use of Tc99m-labelled myocardial perfusion agents should be preferred because of their lower radiation burden.

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 Tl201-thallium 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 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 Tl201-thallium 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 Fertility, pregnancy and lactation

No data are available on the use of Thallous (Tl201) Chloride in pregnancy. According to the high uterus radiation doses, Thallous (Tl201) chloride 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. Where uncertainty exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information.

Breastfeeding
Thallous (Tl201) chloride injection is contraindicated in breast-feeding mothers.

Before administering radiopharmaceuticals to a mother who is breast-feeding consideration should be given as to the possibility of delaying the administration of the radionuclide until the mother has ceased breast-feeding and to what is the most appropriate choice of radiopharmaceuticals bearing in mind the lack of data concerning the secretion of (TL201) 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.

Adverse Reactions sorted by System Organ Class:

Immune system disorders
Frequency unknown*: Anaphylactoid reactions (e.g. laryngismus, pharyngitis, larynx 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, coughing)

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

* Adverse reactions derived from spontaneous reporting

Thallous (Tl201) 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
Local radiation necrosis may occur after paravenous injection.

4.9 Overdose

The risk of overdose lies in a unintentional high exposure to ionising radiation .In the event of the administration of a radiation overdose with thallous (Tl201) 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 (Tl201) chloride may be prevented by administration of the antidote ferric hexacyanoferrate(II).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceutical, cardiovascular group. ATC code: V09GX01.
At the chemical concentrations and activities used for diagnostic procedures. Thallous (Tl201) chloride does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

Distribution
After intravenous injection of thallous (Tl201) 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 Tl201 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 uncertain but the sodium-potassium ATPase pump is probably involved, at least in part. The muscular uptake depends 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 %). 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 8-45 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride and 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

7 days after activity reference time.
After aseptic removal of the first aliquot: 8 hours
Store at 2°C-8°C after aseptic removal of the first aliquot.

6.4 Special precautions for storage

Do not store above 25°C.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

10 ml glass vial (Type 1 Ph.Eur.) closed with a bromobutyl rubber stopper and sealed with an aluminium crimp cap. The glass vial is supplied in a lead shielding.
Thallous (Tl201) chloride injection is supplied in the following amounts at activity reference date and time:
63 MBq in 1.7 ml
85 MBq in 2.3 ml
213 MBq in 5.8 ml
370 MBq in 10.0 ml

6.6 Special precautions for disposal and other handling

General warnings
Radiopharmaceuticals should 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 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.

For instructions on preparation of the medicinal product before administration, see section 12

If at any time in the preparation of this product the integrity of this vial is compromised it 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 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.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Curium Netherlands B.V.
Westerduinweg 3
1755 LE Petten
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

PL 12288/0016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 October 2002

10. DATE OF REVISION OF THE TEXT

20/10/2022

11. DOSIMETRY

Tl201 is cyclotron produced and decays to Hg201 by electron capture with an energy as shown in the table below and a half-life of 73.1.

Gamma-rays	135 keV	(2.7% abundance)
Gamma-rays	166 keV	(1.6% abundance)
Gamma-rays	167 keV	(10.0 % abundance)
X-rays	68 keV	(27.4% abundance)
X-rays	80 keV	(20.5% abundance)

The data listed below are from ICRP 106.
Absorbed dose per unity activity administered (mGy/MBq)

Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	0.057	0.070	0.10	0.15	0.27
Bladders wall	0.039	0.054	0.079	0.12	0.22
Bone surfaces	0.38	0.39	0.69	1.2	1.9
Brain	0.022	0.024	0.036	0.054	0.11
Breast	0.024	0.027	0.044	0.066	0.13
Gall bladder	0.065	0.081	0.13	0.19	0.31
GI-tract					
Stomach	0.11	0.15	0.22	0.35	0.73
Small intestine	0.14	0.18	0.30	0.50	0.94
Colon	0.25	0.32	0.55	0.92	1.8
(ULI	0.18	0.23	0.39	0.64	1.2
LLI)	0.34	0.45	0.76	1.3	2.5
Heart	0.19	0.24	0.38	0.60	1.1
Kidneys	0.48	0.58	0.82	1.2	2.2
Liver	0.15	0.20	0.31	0.45	0.84
Lungs	0.11	0.16	0.23	0.36	0.69
Muscles	0.052	0.082	0.16	0.45	0.76
Oesophagus	0.036	0.042	0.060	0.090	0.16
Ovaries	0.12	0.12	0.29	0.49	2.8
Pancreas	0.057	0.070	0.11	0.16	0.28
Red marrow	0.11	0.13	0.22	0.45	1.1
Skin	0.021	0.024	0.038	0.058	0.11
Spleen	0.12	0.17	0.26	0.41	0.74
Testes	0.18	0.41	3.1	3.6	4.9
Thymus	0.036	0.042	0.002	0.090	0.16
Thyroid	0.22	0.35	0.54	1.2	2.3
Uterus	0.050	0.062	0.099	0.15	0.27
Remaining organs	0.054	0.082	0.16	0.34	0.55
Effective dose (mSv/MBq)	**0.14**	**0.20**	**0.56**	**0.79**	**1.3**

The effective dose resulting from the administration of a (maximal recommended) activity of 110 MBq for an adult weighing 70 kg is about 15 mSv.

For an administered activity of 110 MBq the typical radiation dose to the target organ (myocardium) is 21 mGy and the typical radiation doses to the typical organs (kidney and descending colon) are 53 and 37 mGy, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vial must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using a an authorised automated application system.

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