8 February 2023

SUMMARY OF PRODUCT CHARACTERISTICS

for

Thallous (Tl-201) Chloride Injection, solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Thallous (Tl201) chloride Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 37 MBq thallous (Tl-201) chloride at the date and time of calibration. The specific activity is more than 18.5 GBq/ mg thallium. Tl-201 decays to Hg-201 by electron capture with a half-life of 3.04 days. The energies of the main gamma radiations are 167 keV (10 %) and 135 keV (2.6 %). The energies of X-rays are 69 to 83 keV.

Excipient with known effect:
Each ml of thallous (Tl-201) chloride injection contains 3.5 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless solution with pH 4.0 to 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Thallous (Tl201) Chloride injection is indicated in adults for:

- 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

Posology

Adults and elderly

The recommended activity for a patient of average weight (70 kg) is 50 to 80 MBq of thallous (Tl201) chloride solution, administered by intravenous injection at stress or rest. This activity can be increased by 50 % if SPECT-imaging is considered until a maximum activity of 110 MBq. An additional injection of 40 MBq at rest may be considered after initial stress injection (re-injection).

Paediatric population

Thallous (Tl201) chloride is contraindicated in children and adolescents (see section 4.3).

Renal impairment/hepatic impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Method of administration

For multi-dose use.

Administration is by intravenous injection. The insertion of an intravenous flexible catheter is recommended during the entire examination. The injection must be followed by rinsing the catheter with saline before removing it.

Thallous (Tl201) chloride injection can be done either at rest or during intervention tests (e.g. conventional stress test or pharmacological test).

For instructions for preparation of the medicinal product, see section 12.

For patient preparation, see section 4.4.

Image acquisition

Myocardial Scintigraphy:

Acquisition can be performed 5 to 10 minutes after injection by gated or non-gated SPECT acquisition.

Thallium redistribution can be studied with a new set of images acquisition obtained between 3 to 4 hours after injection. In some cases, instead of the redistribution study (or after it), re-injection of 40 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 the active substance or to any of the excipients listed in section 6.1.
- Pregnancy
- Breastfeeding women
- Children below the age of 18 years
- 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.

Renal/hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Patient preparation
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 examination in order to reduce radiation.

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

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

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

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 warmed and rested in elevated position. When radiation necrosis occurs, surgical intervention may be necessary.

Specific warnings
This medicinal product contains 3.5 mg of sodium per ml. Sodium content should be taken into account in case a dose of more than 6.5 ml (equivalent to 23 mg of sodium) is administered to a patient on a low sodium diet.

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

In the case of **pharmacological exposure** to a vasodilator (e.g. adenosine, dipyridamole, or regadenoson), methylxanthines (e.g. caffeinated drinks, antimigraine medications, and theophylline) should not be consumed for at least 12 hours prior to the exposure test. Drugs containing dipyridamole should also be discontinued for at least 24 hours.

In the case of **pharmacological exposure** to ino/chronotropic agent (e.g. dobutamine), beta-blockers should be discontinued before the procedure. Atropine may be required to increase heart-rate response.

In the case of **ergometric stress test**, anti-anginal drugs can mask exercise-induced ischemia (e.g. beta-blockers, calcium antagonists and nitrates). They should be discontinued for at least 24 hours. Sublingual nitroglycerin can be taken up to 2 hours before exercise.

If the effectiveness of antianginal therapy is to be documented with myocardial perfusion scintigraphy, it makes sense to carry out the examination with ongoing medication.

Digoxin may reduce the uptake of thallium (Tl-201) to the myocard although no definitive data are available.

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 thallous (Tl201) chloride in pregnancy. The use of thallous (Tl201) chloride is contraindicated in pregnant women due to the high uterus radiation doses (see section 4.3).

Breastfeeding
Thallous (Tl201) chloride injection may be excreted in breast milk and is therefore contraindicated in breastfeeding mothers.

Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given as 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 radiopharmaceuticals bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 48 hours and the expressed feeds discarded.

Fertility
No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

Thallous (Tl201) chloride has no or negligible influence on the ability to drive and use machines.

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 following list subsumes the observed reaction types and symptoms sorted by System Organ Class. The frequency listed below is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Immune system disorders
Frequency not known*: Anaphylactoid 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, hyperhidrosis, cough).

Nervous system disorders
Frequency not known*: Vasovagal reactions (e.g. syncope, dizziness, bradycardia, hypotension, tremor, headache, pallor).

General disorders and administration site conditions
Frequency not known*: Injection site reaction.

Injury, poisoning and procedural complications
Frequency not known*: Local radiation necrosis after paravenous injection.

* 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 21 mSv when the maximal recommended activity of 150 MBq is administered these adverse reactions 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:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Websted: www.meldenbivirkning.dk

4.9 Overdose

The risk of overdose lies in an unintentional high exposure to ionising radiation. In the event of 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 and 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 used for diagnostic examinations, thallous (Tl201) chloride does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

<u>Distribution</u>
After intravenous injection of thallous (Tl201) chloride, the thallium rapidly leaves the blood as approximately 90 % is cleared after the first pass.

<u>Organ uptake</u>
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. The maximum accumulation in the normal heart muscle is reached about 10 minutes after the injection at rest and about 5 minutes after the injection under stress. It remains relatively constant for about 20-25 minutes. The distribution in the myocardium clearly correlates with the local blood flow. In myocardial areas with impaired blood flow, ischemia or infarction, Thallium-201 is stored less or not at all. The half-life of cardiac (Tl201) thallium clearance is 4.4 hours.
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.

<u>Elimination</u>
Thallium is mainly excreted in the faeces (80 %) and in the urine (20 %). Persistent radioactivity has been observed after 24 h especially in kidneys, colon and testes.

<u>Half-life</u>
The physical half-life is 3.04 days, the biological half-life about 10 days and the effective half-life is about 60 hours.

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.
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
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

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.
Store at 2°C-8°C after aseptic removal of the first aliquot.

Chemical and physical in-use stability has been demonstrated for 8 hours at 2°C - 8°C.
From a microbiological point of view, unless the method of opening and withdrawal precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after first opening of the medicinal product, see section 6.3.
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 I 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 (Tl-201) 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

Not all pack sizes may be marketed.

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 licences 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.

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 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

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

8. MARKETING AUTHORISATION NUMBER

DK R 1000

9. DATE OF FIRST AUTHORISATION

31 January 1995

10. DATE OF REVISION OF THE TEXT

8 February 2023

11. DOSIMETRY

According to Publication 128 of the ICRP (International Commission on Radiological Protection), doses of radiation absorbed by patients are as follows:

Organ	**Absorbed dose per unit activity administered (mGy/MBq)** **Adult**
Adrenals	0.057
Bone surfaces	0.38
Brain	0.022
Breast	0.024
Gall bladder wall	0.065
GI-tract	
Stomach wall	0.11
Small intestine wall	0.14
Colon wall	0.25
(ULI wall	0.18
LLI wall)	0.34
Heart wall	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
Urinary bladder wall	0.039
Uterus	0.050
Remaining organs	0.054
Effective dose (mSv/MBq)	**0.14**

The effective dose resulting from the administration of a (maximal recommended) activity of 150 MBq for an adult weighing 70 kg is about 21 mSv.
For an administered activity of 150 MBq the typical radiation dose to the target organ (myocardium) is 29 mGy and the typical radiation doses to the critical organs (kidney and descending colon) are 72 and 51 mGy, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Ready for use. No preparation needed.

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 an authorised automated application system.

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