PRODUCT MONOGRAPH

THALLOUS CHLORIDE Tl 201 INJECTION

Thallium Tl 201

Solution for intravenous use containing per mL, 37 megabecquerels (1 millicurie) Thallous Chloride Tl 201 at calibration time.

Radiodiagnostic Agent

Date of Revision: April 26th, 2019

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Control number: 225111

Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

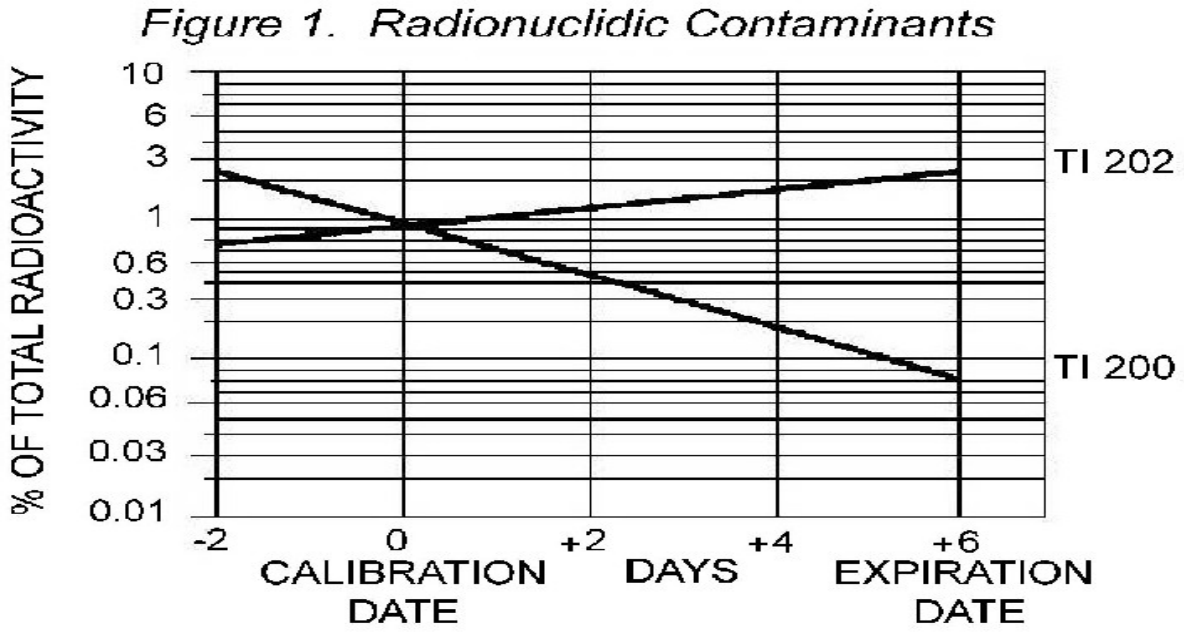
SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous injection.	Solution containing 37 megabecquerels (1 millicurie) per mL, Thallous Chloride Tl 201 at calibration time.	Solution containing per mL, 9 mg Sodium Chloride and preserved with 0.9% benzyl alcohol. Sodium Hydroxide and Hydrochloric Acid may be added for pH adjustment. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

It is recommended that Thallous Chloride Tl 201 be administered close to calibration time to minimize the effect of higher levels of radionuclidic contaminants present at pre- and post-calibration dates. The concentration of each radionuclidic contaminant changes with time. Figure 1 shows maximum concentration of each radionuclidic contaminant as a function of time.

Figure 1. Radionuclidic Contaminants



Physical Characteristics

Thallium Tl 201, with a physical half life of 73.1 hours, decays by electron capture to mercury Hg 201. [1] Photons that are useful for detection and imaging are listed in Table 1. The lower energy x-rays obtained from the mercury Hg 201 daughter of Thallium Tl 201 are recommended for myocardial imaging, because the mean percent disintegration at 68.9 to 80.3 keV is much greater than the combination of gamma-4 and gamma-6 mean percent disintegration.

Table 1. Principal Radiation Emission Data[1]

Radiation	Mean Percent / Disintegration	Energy (keV)
Gamma-4	2.7	135.3
Gamma-6	10.0	167.4
Mercury (x-rays)	94.4	68.9-80.3

External Radiation

The specific gamma ray constant for Thallium Tl 201 is 4.7R/mCi-hr* at 1 cm. The first half-value thickness of lead (Pb) is 0.0006 cm. A range of values for the radiation emitted by this radionuclide with the corresponding exposure rate at 1 cm that results from interposition of various thicknesses of lead is shown in Table 2. For example, the use of 0.21 cm of lead will decrease the external radiation exposure by a factor of about 1,000.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness (Pb), cm	Coefficient of Attenuation
0.0006	0.5
0.015	10^{-1}
0.098	10^{-2}
0.21	10^{-3}
0.33	10^{-4}

* Includes 10 keV x-rays.

To correct for physical decay of the radionuclide, the fractions that remain at selected intervals after calibration time are shown in Table 3.

Table 3. Thallium Tl 201 Decay Chart; Half-Life 73.1 Hours

Hours	Fraction Remaining		Hours	Fraction Remaining
0*	1.00		66	0.53
6	0.94		72	0.51
12	0.89		78	0.48
18	0.84		84	0.45
24	0.80		90	0.43
30	0.75		96	0.40
36	0.71		108	0.36
42	0.67		120	0.32
48	0.63		132	0.29
54	0.60		144	0.26
60	0.57			

* Calibration Time

INDICATIONS AND CLINICAL USE

Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging using either planar or SPECT (Single Photon Emission Computed Tomography) techniques for the diagnosis and localization of myocardial infarction. It may also have prognostic value regarding survival, when used in the clinically stable patient following the onset of symptoms of an acute myocardial infarction, to assess the site and size of the perfusion defect.

Thallous Chloride Tl 201 may also be useful in conjunction with exercise stress testing as an adjunct to the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

Thallous Chloride Tl 201 is also indicated for scintigraphic imaging of the myocardium to identify changes in perfusion induced by pharmacologic stress *(with adenosine or dipyridamole)* in patients with known or suspected coronary artery disease and who cannot exercise adequately.

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

Thallous Chloride Tl 201 is indicated also for the localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels. It may also be useful in pre-operative screening to localize extrathyroidal and mediastinal sites of parathyroid hyperactivity and for postsurgical reexamination. Thallous Chloride Tl 201 has not been adequately demonstrated to be effective for the localization of normal parathyroid glands.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. [if applicable]
- There are no other known contraindications for Thallium Tl 201.

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions

- Pharmacologic induction of cardiovascular stress may be associated with serious adverse events such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction and cerebrovascular events. Caution should be used when pharmacologic stress is selected as an alternative to exercise; it should be used when indicated and in accordance with the pharmacologic stress agent's labeling.
- Thallous Chloride Tl 201 should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus (see WARNINGS AND PRECAUTIONS – Pregnant Women).
- Thallous Chloride Tl 201 is distributed into breast milk. To avoid unnecessary irradiation of the infant, formula feeding should be substituted temporarily for breast feeding (see WARNINGS AND PRECAUTIONS – Nursing Women).
- Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans (see Indications and Clinical Use section).

General

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

This drug should not be used after six (6) days from the calibration date, or nine (9) days from date of manufacture, whichever comes first.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides.

When studying patients suspected or known to have myocardial infarction or ischemia, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedures. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Data are not available concerning the effect on the quality of Thallous Chloride Tl 201 images of marked alterations in blood glucose, insulin or pH (such as is found in diabetes mellitus). Attention is directed to the fact that Thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the Thallous Chloride Tl 201 may likewise be affected.

Repeat procedures: The safety of repeated doses has not been studied.

Carcinogenesis and Mutagenesis

No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenic potential or whether this drug affects fertility in males or females.

Cardiovascular

The following medical considerations/contraindications have been selected on the basis of their potential clinical significance where a risk-benefit assessment should be carried out prior to administering Thallous Chloride Tl 201. These medical considerations/contraindications may not be inclusive of all clinical situations where a risk-benefit assessment should be considered.

For adenosine/thallium or dipyridamole/thallium stress test:

- >> Hypotension due to an increased risk of severe hypotension.
- >> History of unstable angina due to increased risk of severe myocardial ischemia.

For adenosine/thallium stress test:

- >> Pre-existing second or third degree Atrioventricular (AV) block;
- >> Severe congestive heart failure;
- >> Severe ischemic cardiomyopathy;
- >> Recent myocardial infarction due to increased risk of severe myocardial ischemia and/or arrhythmia.

Immune

Hypersensitivity to the radiopharmaceutical preparation has been reported previously. Patients with a history of allergy or drug reaction should be observed for several hours after drug administration. The possibility of a reaction, including serious, life threatening, fatal anaphylactoid or cardiovascular reactions or other idiosyncratic reactions, should always be considered especially in those patients with a known clinical hypersensitivity (see ADVERSE REACTIONS).

Respiratory
Risk-benefit should be considered when the following medical problems exist:

>> For adenosine/thallium or dipyridamole/thallium stress test, history of bronchospastic pulmonary disease due to an increased risk of bronchospasm;

>> For dipyridamole/thallium stress test, current or history of asthma due to increased risk of bronchospasm.

Sexual Function/Reproduction
No long-term animal studies have been performed to evaluate this drug's effects on fertility in males or females.

Special Populations

Pregnant Women: Animal reproductive studies have not been conducted with Thallous Chloride Tl 201. It is also not known whether Thallous Chloride Tl 201 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Studies to assess transplacental transfer of Thallous Chloride Tl 201 have not been done in humans.
Assess the pregnancy status of women of childbearing potential prior to performing imaging procedures with Thallous Chloride Tl 201 Injection**.**

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of women of childbearing capability should be performed during the first ten days following the onset of menses.

Thallous Chloride Tl 201 should not be given to a pregnant woman unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.

Nursing Women: Thallous Chloride Tl 201 is distributed into breast milk. To avoid unnecessary irradiation of the infant, temporary discontinuation of nursing is recommended for a minimum period of 96 hours.

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients below age 18 have not been established.

Geriatrics (> *65* years of age): Although published clinical studies have not identified a difference in diagnostic accuracy and safety between subjects aged over 65 and younger subjects undergoing Thallous Chloride Tl 201 myocardial perfusion imaging with pharmacologic stress testing, studies have not included sufficient numbers of subjects aged over 65 in order to determine whether they respond differently from younger subjects.

Since Thallous Chloride Tl 201 is substantially excreted by the kidney, and elderly patients are more likely to have decreased renal function, care should be taken in dose selection and monitoring for renal adverse drug reactions in this patient population.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Following the administration of Thallous Chloride Tl 201, adverse anaphylactoid reactions have been reported (characterized by cardiovascular, respiratory, and cutaneous symptoms), some severe enough to require treatment. Hypotension, pruritus, flushing, and diffuse rash which respond to antihistamines have been reported. Other reported events include itching, nausea/vomiting, mild diarrhea, tremor, shortness of breath, chills, fever, conjunctivitis, sweating, blurred vision and injection site reaction.

Adverse events, some of which were serious, have also been reported in patients who have undergone thallium pharmacologic stress testing (see WARNINGS AND PRECAUTIONS). Please refer to the product monographs of approved pharmacologic stress agents for more detailed information on those adverse reactions.

Clinical Trial Adverse Drug Reactions

A variety of non-cardiac side effects are observed with dipyridamole use including headache (12%), dizziness, nausea, vomiting and flushing (12%), while cardiac related side effects such as chest pain (20%) and ST depression (7.5%) are normally less severe than with exercise stress. Severe side effects remain rare with non-fatal myocardial infarction estimated to occur in only 0.1% of patients.

The non-cardiac side effects observed with adenosine use include headaches (85%), flush (29%), chest and throat or jaw pain (57%). Ischemic electrocardiogram changes may be observed in a significant number of patients.

Adverse drug reactions were not reported in association with Thallous Chloride Tl 201 in the pharmacologic stress studies.

Abnormal Hematologic and Clinical Chemistry Findings

Hematologic and clinical chemistry investigations have not been carried out in clinical studies following administration of Thallous Chloride Tl 201.

Post-Market Adverse Drug Reactions

These are similar to those listed in the Adverse Drug Reaction Overview above.

DRUG INTERACTIONS

Drug-Drug Interactions

Specific drug-drug interactions have not been studied in humans.

In animal studies, concurrent use of the following drugs increased myocardial uptake of Thallous Chloride Tl 201; dexamethasone, furosemide, and isoproterenol.

In animal studies, concurrent use of the following drugs decreased myocardial uptake of Thallous Chloride Tl 201; digital glycosides and propranolol.

Xanthine-derivative medications and caffeine antagonize the effects of adenosine and dipyridamole on myocardial blood flow. Xanthine-derivative medications should be withheld for 24 to 36 hours, and patients should be instructed to avoid ingesting caffeine-containing products for 8 to 12 hours prior to the Thallous Chloride Tl 201 pharmacologic stress test.

Drug-Food Interactions
Increased accumulation of Thallous Chloride Tl 201 in the abdominal viscera (stomach, liver, spleen, and intestines), in the postprandial state may interfere with myocardial visualization during the resting, exercise, or pharmacologic stress test.

Drug-Herb Interactions
No interactions with herbal products have been studied.

Drug-Laboratory Interactions
No interactions with laboratory tests have been established.

Drug-Lifestyle Interactions
When utilized in conjunction with exercise stress testing, investigators have reported that within two hours after the completion of stress testing, the target-to-background ratios may decrease significantly in lesions that are attributable to transient ischemia.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Parental drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if contents are turbid.

- Waterproof gloves should be worn during the handling procedures.

Dosage
The recommended adult dose of intravenous Thallous Chloride Tl 201 for planar myocardial imaging is 37 to 74 MBq (1-2 mCi). The recommended intravenous doses for SPECT myocardial imaging are 74 to 111 MBq (2-3 mCi). The efficacy of a 1.0 mCi dose for SPECT imaging has not been well established.

Administration
The patient dose should be measured by a suitable radioactivity calibration system prior to administration.

With a shielded sterile syringe, aseptically withdraw the material for use.

For resting Thallous Chloride Tl 201 studies, imaging should begin 10 to 20 minutes after injection. Myocardial-to-background ratios are improved when patients are injected upright and in the fasting state; the upright position reduces the hepatic and gastric Thallium Tl 201 concentration.

When utilized in conjunction with exercise stress testing, Thallous Chloride Tl 201 should be administered at the inception of a period of maximum stress which is sustained for approximately 30 seconds after injection. Imaging should begin within ten minutes after administration to obtain maximum target-to-background ratios. Several investigators have reported that within two hours after the completion of stress testing the target-to-background ratios may decrease significantly in lesions that are attributable to transient ischemia.

When utilized in conjunction with pharmacological stress agents, the dose of either dipyridamole or adenosine is routinely adjusted to the weight of the patient and infused using a dose rate of 0.14 mg/kg/minute over a four minute period or six minute period, respectively. The total administered dose of dipyridamole is approximately 0.56 mg per kg and that or adenosine is approximately 0.84 mg per kg. Thallous Chloride Tl 201 is then injected as a bolus 3 – 4 minutes after the infusion of the pharmacological stress agent. PLEASE CONSULT THE FULL DOSING INSTRUCTIONS IN THE PRODUCT MONOGRAPHS OF THE PHARMACOLOGIC STRESS AGENTS BEFORE PROCEEDING WITH THE STRESS TEST.

Image Acquisition and Interpretation

For the localization of parathyroid hyperactivity, Thallous Chloride Tl 201 may be administered before, with or after a minimal dose of a thyroid imaging agent such as sodium pertechnetate Tc 99m or sodium iodide I 123 to enable thyroid subtraction imaging.

Instructions for Preparation and Use

The components of the reagent vial are sterile and non-pyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic technique.

Use aseptic technique and wear waterproof gloves throughout the entire preparation procedure.

Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.

Directions for Quality Control

The radiochemical purity of the radiopharmaceutical product should be determined prior to administration to the patient.

RADIATION DOSIMETRY

The estimated absorbed radiation doses[3] at calibration time to an average patient (70 kg) from an intravenous injection of Thallous Chloride Tl 201 are shown below.

Example of Acceptable Presentation of Dose Estimate Data:

Table 4. Radiation Dose Estimates for Tl 201 Chloride (plus contaminants)

	mGy/MBq	rad/mCi
ORGAN		
Adrenals	6.2E-02	2.3E-01
Brain	5.9E-02	2.2E-01
Breasts	3.6E-02	1.3E-01
Gallbladder Wall	8.3E-02	3.1E-01
LLI Wall	3.4E-01	1.2E+00
Small Intestine	4.5E-01	1.7E+00
Stomach	1.9E-01	6.9E-01
ULI Wall	3.3E-01	1.2E+00
Heart Wall	2.8E-01	1.0E+00
Kidneys	4.6E-01	1.7E+00
Liver	9.9E-02	3.7E-01
Lungs	4.7E-02	1.7E-01
Muscle	4.6E-02	1.7E-01
Ovaries	1.0E-01	3.7E-01
Pancreas	7.4E-02	2.7E-01
Red Marrow	5.5E-02	2.0E-01
Bone Surfaces	8.8E-02	3.3E-01
Skin	3.3E-01	1.2E-01
Spleen	1.8E-01	6.5E-01
Testes	8.2E-01	3.0E+00
Thymus	4.6E-02	1.7E-01
Thyroid	6.2E-01	2.3E+00
Urinary Bladder Wall	5.2E-02	1.9E-01
Uterus	8.5E-02	3.1E-01
Effective Dose	3.6E-01/	1.3E+00
Equivalent	mSv/MBq	rem/mCi

Based on data gathered in humans by Krahwinkel et al. (J Nucl Med 29 (9):1582-1586, 1988) and data gathered in humans by Gupta et al (Int J Nucl Med & Biol 8:211-213, 1981).

Table 5. Assumed Distribution and Retention

ORGAN		
Brain	1.76% $T_b = \infty$	
LLI	3.6% T_b = 191 hr	(Activity in Wall)
Small Intestine	14.4% T_b = 191 hr	(Activity in Wall)
Stomach	2.8% T_b = 205 hr	(Activity in Wall)
ULI	4.7% T_b = 191 hr	(Activity in Wall)
Heart Wall	3.4% T_b = 179 hr	
Kidneys	4.5% T_b = 260 hr	0.97% T_b = 27 hr
Liver	4.6% T_b = 218 hr	
Spleen	0.74% T_b = 640 hr	0.28% T_b = 37 hr
Testes	1.0% $T_b = \infty$	
Thyroid	0.29% T_b = 350 hr	0.24% T_b = 166 hr
Total Body	31% T_b = 146 hr	69% T_b = 502 hr
Urinary Bladder Clearance	6.2% T_b = 146 hr	13.8% T_b = 502 hr

Bladder voiding interval 4.8 hr. Contaminants assumed: Tl 200 (1%), Tl 202 (0.33%), Pb 201 (0.33%), Pb 203 (0.33%). Includes dose from Tl 201 Auger electrons. Estimate calculated using phantom of Cristy & Eckerman (Report ORNL/TM-8381/V1 & V7).

OVERDOSAGE

Cases of overdose are not known to have occurred with Thallous Chloride Tl 201 Injection. In case of overdose, the patient should be monitored clinically for symptoms consistent with adverse drug reactions attributable to Thallous Chloride Tl 201. Patients should be managed symptomatically as needed, based on symptoms.

In the event of the administration of a radiation overdose with thallium Tl-201, 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 gastrointestinal passage.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Thallous Chloride Tl 201 with no carrier added has been found to accumulate in viable myocardium in a manner analogous to that of potassium. Experiments in human volunteers using labelled microspheres have shown that the myocardial distribution of Thallous Chloride Tl 201 correlates well with regional perfusion.

In clinical studies, Thallous Chloride Tl 201 images have been found to visualize areas of infarction as "cold" or non-labeled regions which are confirmed by electrocardiographic and enzyme changes. When the "cold" or non-labeled regions comprise a substantial portion of the

left ventricle, the prognosis for survival is unfavorable. Regions of transient myocardial ischemia corresponding to areas perfused by coronary arteries with partial stenoses have been visualized when Thallous Chloride Tl 201 was administered in conjunction with an exercise stress test. Anatomic configurations may interfere with visualization of the right coronary artery.

Pharmacodynamics

The Pharmacodynamics of Thallous Chloride Tl 201 has not been established.

Pharmacokinetics

Distribution

After intravenous administration, Thallous Chloride Tl 201 clears rapidly from the blood with maximal concentration by normal myocardium occurring at about 10 minutes. It will, in addition, localize in parathyroid adenomas; it is not specific since it will localize to a lesser extent in sites of parathyroid hyperplasia and other abnormal tissues such as thyroid adenoma, neoplasia (e.g., parathyroid carcinoma) and sarcoid. Biodistribution is generally proportional to organ blood flow at the time of injection. Blood clearance of Thallous Chloride Tl 201 is primarily by the myocardium, thyroid, liver, kidneys and stomach with the remainder distributing fairly uniformly throughout the body. The dosimetry data in Table 4 reflect this distribution pattern and are based on a biological half-life of 2.4 days. Thallous Chloride Tl 201 is excreted slowly and to an equal extent in both feces and urine.

Metabolism

Five minutes after intravenous administration only 5 to 8 percent of injected activity remained in the blood. A biexponential disappearance curve was obtained, with 91.5 percent of the blood radioactivity disappearing with a half-time of about 5 minutes. The remainder had a half-time of about 40 hours.

Excretion

Approximately 4 to 8 percent of the injected dose was excreted in the urine in the first 24 hours. The whole body disappearance half-time was 9.8 ± 2.5 days. Kidney concentration was found to be about 3 percent of the injected activity and the testicular content was 0.15 percent. Net thyroid activity was determined to be only 0.2 percent of the injected dose, and the activity disappeared in 24 hours. From anterior and posterior whole-body scans, it was determined that about 45 percent of the injected dose was in the large intestines and contiguous structures (liver, kidneys, abdominal musculature).[2]

Special Populations and Conditions

The pharmacokinetics of Thallous Chloride Tl 201 have not been established in special populations and conditions.

STORAGE AND STABILITY

Store this drug at controlled room temperature, 20-25°C (68-77°F). The expiry for the kit is 9 days after the date of manufacture and after standardization, it is 6 days. Storage and disposal of Thallous Chloride Tl 201 Injection should be controlled in a manner that is in compliance with the appropriate regulations of the government agency authorized to license the use of this radionuclide.

SPECIAL HANDLING INSTRUCTIONS

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Catalog Number 120

Thallous Chloride Tl 201 is supplied in a sterile, non-pyrogenic solution for intravenous administration. Each mL contains 37 MBq (1 mCi) Thallous Chloride Tl 201 at calibration time, 9 mg sodium chloride and 0.9 percent (v/v) benzyl alcohol. The pH is adjusted to between 4.5 to 7.0 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 103.6, 207.2, 233.1, 366.3 megabecquerels (2.8, 5.6, 6.3 and 9.9 millicuries) of Thallium Tl 201.

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

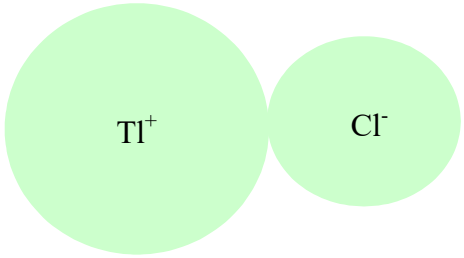
Drug Substance

Proper name: Thallium Tl 201

Chemical name: Thallous Chloride Tl 201

Molecular formula and molecular mass: TlCl, molecular mass is 239.836

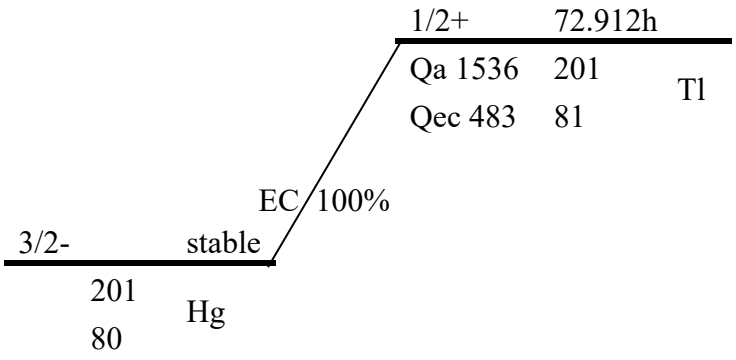
Structural formula:



Physicochemical properties:

Color: White
Appearance: Crystalline solid
Melting Point: 430°C
Boiling Point: 720°C
Density: 7004 kg m^{-3}

Radioactive Properties
The physical decay scheme of ^{201}Tl is:



The physical half-life of ^{201}Tl is 72.912h and ^{201}Hg is a stable isotope.

Product Characteristics
Thallous Chloride Tl 201 Injection is supplied in an isotonic solution as a sterile, non-pyrogenic diagnostic radiopharmaceutical for intravenous administration. Each milliliter contains 37 megabecquerels (1 millicurie) Thallous Chloride Tl 201 at calibration time, made isotonic with 9 milligrams sodium chloride and preserved with 0.9% (v/v) benzyl alcohol. The pH is adjusted to between 4.5 to 7.0 with hydrochloric acid and/or sodium hydroxide. Thallium Tl 201 is cyclotron produced. At the time of calibration it contains no more than 1.0% Thallium Tl 200, no more than 1.0% Thallium Tl 202, no more than 0.25% Lead Pb 203, and no less than 98% Thallium Tl 201 as a percentage of total activity. No carrier has been added.

CLINICAL TRIALS

Curium has conducted an extensive, well-defined search of the scientific literature and performed a meta-analysis of appropriate articles dealing with the sensitivity and specificity of Tl 201 used in combination with the pharmacologic stress agents dipyrimadole and adenosine. The analysis objective for accepted articles was to assess the diagnostic value of thallium 201 scintigraphy in conjunction with vasodilator pharmacologic stress in the detection of CAD. Coronary angiography was used as the gold standard for determining the presence and severity of coronary artery disease. A total of 2614 subjects from 25 studies were included in the analysis. A total of 1217 patients (14 studies) received dipyridamole, while 1397 patients (11 studies) received adenosine. Two study subgroups were established for each agent based on the severity of coronary stenosis as determined by angiography luminal area narrowing >70% and luminal area narrowing >50%. These meta-analyses included patients who were known to have, or suspected of having, CAD, which may have inflated sensitivity and underestimated specificity

Table 6. Sensitivity and Specificity of Dipyridamole or Adenosine Thallium 201 Scintigraphy in Diagnosing CAD

	Stenosis ≥70% N = 913		**Stenosis ≥50% N=304**	
	% Sensitivity [95% CI]	**% Specificity [95% CI]**	**% Sensitivity [95% CI]**	**% Specificity [95% CI]**
Dipyridamole (Fixed Effects Model)	91.45% [89.39, 93.51]	76.61% [71.10, 82.11]	89.20% [85.21, 93.20]	68.41% [58.45, 78.36]
Dipyridamole (Random Effects Model)	90.60% [87.60, 93.61]	76.60% [71.07, 82.12]	89.31% [85.01, 93.58]	64.18% [49.71, 86.99]
	Stenosis ≥70% N = 112		**Stenosis ≥50% N=1345**	
	% Sensitivity [95% CI]	**% Specificity [95% CI]**	**% Sensitivity [95% CI]**	**% Specificity [95% CI]**
Adenosine (Fixed Effects Model)	93.25% [88.02, 98.49]	100.00% [86.80, 100.00]	88.77% [86.86, 90.67]	90.06% [86.34, 93.78]
Adenosine (Random Effects Model)	93.25% [88.02, 98.49]	100.00% [86.80, 100.00]	88.81% [86.31,91.30]	88.56% [82.40, 94.72]

For dipyridamole stress/rest Tl 201 myocardial perfusion studies, 8 of 14 studies in the meta-analysis used limited exercise in conjunction with this pharmacologic stress agent, including hand-grip test, walk in place, and leg swinging. Limited exercise, as compared to no exercise, did not appear to alter the diagnostic accuracy of Thallous Chloride Tl 201.

The specificity of Thallous Chloride Tl 201 for planar imaging with adenosine pharmacologic stress is unknown since limited data were available for planar imaging.

DETAILED PHARMACOLOGY
See ACTION AND CLINICAL PHARMACOLOGY in PART I of the Product Monograph

TOXICOLOGY
Toxicological studies have not been carried out with Thallous Chloride Tl 201.

REFERENCES

1. Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC – 11026, 181 (1981).

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PART III: CONSUMER INFORMATION
Thallous Chloride Tl 201 Injection
Thallium Tl 201

This leaflet is part III of a three-part "Product Monograph" published when Thallous Chloride Tl 201 Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Thallous Chloride Tl 201 Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Thallous Chloride Tl 201 is a diagnostic radiopharmaceutical used for imaging with a special camera located in the nuclear medicine department of a hospital or heart clinic. Thallous Chloride Tl 201 is used for:

- Imaging the heart in patients who have had a heart attack
- Imaging an overactive parathyroid gland in certain patients
- Imaging the heart in patients who suffer from heart disease caused by narrowing of blood vessels in the heart. To better detect the diseased vessels, a stress test is carried out using either exercise, or the drugs adenosine or dipyridamole in patients who cannot exercise.

Your doctor will use the results of the imaging test to help determine your diagnosis.

What it does:
After being injected in a vein, Thallous Chloride Tl 201 follows the blood supply in your body.

When assessing the heart, if the imaging test shows a decrease in the concentration of Thallous Chloride Tl 201 in your heart, this may indicate to your doctor that you have heart disease.

When assessing the parathyroid gland, if the imaging test shows an increase in the concentration of Thallous Chloride Tl 201 in your parathyroid gland, this may indicate to your doctor that you have an overactive gland.

When it should not be used:
Thallous Chloride Tl 201 may not be given to you if you are allergic to this radiopharmaceutical.

What the medicinal ingredient is:
Thallium Tl 201 is the active ingredient.

What the important nonmedicinal ingredients are:
Benzyl Alcohol
Hydrochloric Acid
Sodium Chloride
Sodium Hydroxide

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Because Thallous Chloride Tl 201 is a radiopharmaceutical, it can only be given to you by doctors and other health professionals who are specially trained and experienced in the safe use and handling of radioisotopes.**
- **If you cannot exercise, the drugs adenosine or dipyridamole may be given to you instead in order to carry out the stress test with Thallous Chloride Tl 201. You could experience side effects from adenosine or dipyridamole, such as a heart attack, problems with your heart beat, decreased blood pressure, difficulty breathing, or stroke. Your doctor will decide whether the use of these drugs is appropriate for you.**
- **Thallous Chloride Tl 201 should not be given to you if you are pregnant; unless your doctor considers that the benefit to you outweighs the potential hazards to the fetus.**
- **Thallous Chloride Tl 201 is known to pass into breast milk during nursing. After receiving this radiopharmaceutical, you should stop breast-feeding for at least 4 days and feed your baby with formula instead during this period.**

BEFORE you receive Thallous Chloride Tl 201 talk to your doctor or pharmacist if:

- You had an allergic reaction to this radiopharmaceutical in the past.
- There is a possibility that you may be pregnant.
- You are breast-feeding your baby.

Your doctor may ask you to do the test on an empty stomach.

After you receive the radiopharmaceutical, use the toilet instead of the urinal and flush it several times after use in order to decrease the risk of radioactive contamination from your urine.

INTERACTIONS WITH THIS MEDICATION

It is unknown whether other drugs interact with Thallous Chloride Tl 201. Talk to your doctor or pharmacist if you are taking any medications.

PROPER USE OF THIS MEDICATION

You will be given Thallous Chloride Tl 201 Injection under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Serious allergic reactions with symptoms such as shortness of breath, swelling of the face, lips, tongue and/or throat, decreased blood pressure, rash, and itching, have been reported with Thallous Chloride Tl 201. Call your doctor if you experience an allergic reaction.

Other reactions that have occurred with Thallous Chloride Tl 201 include nausea, vomiting, mild diarrhea, tremors, chills, fever, pink eye, sweating, blurred vision and reaction at the site where the medication is injected.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Call your doctor or pharmacist
		Only if severe	In all cases	
Common	Nausea		√	
	Diarrhea			
	Tremors	√		
	Chills, fever		√	
	Blurred vision		√	
	Reaction at injection site		√	
	Shortness of breath		√	
Uncommon	Cardiovascular		√	√
	Nervous		√	
	Respiratory		√	√
	Haematology		√	

This is not a complete list of side effects. If you have any unexpected effects after receiving Thallous Chloride Tl 201 Injection, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**

  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, ON K1A 0K9

You can also report suspected adverse reactions directly to Curium Canada Inc. by one of the following 2 ways:

- **Call (toll-free) to 1-866-789-2211**
- **Mail to: Curium Canada Inc.**
  c/o Pharmacovigilance Department
  2572 boul. Daniel-Johnson suite 248
  Laval, QC, H7T-2R3

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals is included with the product or may be obtained by contacting the sponsor, Curium Canada Inc. at 1-866-885-5988.

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Laval, QC, Canada, H7T-2R3

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