AUSTRALIAN PRODUCT INFORMATION

ULTRATAG™ RBC (STANNOUS CHLORIDE DIHYDRATE) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Stannous chloride dihydrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultratag™ RBC Kit for the Preparation of Technetium Tc 99m-Labelled Red Blood Cells, a diagnostic radiopharmaceutical agent.

Ultratag RBC is a sterile, non-pyrogenic, diagnostic kit for the *in vitro* preparation of Technetium Tc 99m-Labelled Red Blood Cells.

Each kit consists of three separate non-radioactive components. A reaction vial containing the active ingredient stannous chloride dihydrate, the contents of the vial are lyophilised and stored under argon. There are two syringes containing diluent solutions for reconstitution.

For the full list of excipients, see section **6.1 LIST OF EXCIPIENTS**.

Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] The principal photon that is useful for detection and imaging is listed in **Table 1**.

Table 1. Principal Radiation Emission Data[1]

Radiation M	**Mean Percent/ Disintegration**	**Energy (keV)**
Gamma-2	89.07	140.5

The specific gamma ray constant for Technetium Tc 99m is 0.78 R/mCi-hr at 1 cm. The first half-value thickness of lead (Pb) for Technetium Tc 99m is 0.017 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide resulting from the interposition of various thicknesses of lead (Pb) is presented in **Table 2**. For example, the use of 0.25 cm of lead will decrease the external radiation exposure by a factor of about 1000.

[1] Kocher, David C., "Radioactive Decay Data Tables," DOE/TIC-11026, 108 (1981).

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

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

Table 3. Physical Decay Chart: Technetium Tc 99m, Half-life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

*Calibration Time

3 PHARMACEUTICAL FORM

Reaction vial: Powder for injection.
White lyophilised powder.
Syringe I: Diluent, Clear colourless liquid.
Syringe II: Diluent, Clear colourless liquid.

4 CLINCIAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Technetium Tc 99m-Labelled Red Blood Cells are used for blood pool imaging, including cardiac first pass and gated equilibrium imaging and for detection of sites of gastrointestinal bleeding.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage
The suggested dose range of Technetium Tc 99m-Labelled Red Blood Cells in the average patient (70 kg) is 370 MBq (10 mCi) to 740 MBq (20 mCi).

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

Radiation Dosimetry
The estimated radiation doses to an average adult (70 kg) from an intravenous injection of a maximum dose of 740 megabecquerel (MBq) (20 millicurie [mCi]) of Technetium Tc 99m-Labelled Red Blood Cells are shown in **Table 4**.

These radiation absorbed dose values were calculated using the Medical Internal Radiation Dose (MIRD) Committee Schema.

Table 4. Absorbed Radiation Dose Estimates[2] for Ultratag RBC

*Technetium Tc 99m-Labelled Red Blood Cells**

Organ	mGy/740 MBq	Rad/20 mCi
Total Body	3.0	0.30
Spleen	22	2.2
Bladder Wall	4.8	0.48
Testes	2.2	0.22
Ovaries	3.2	0.32
Blood	8.0	0.80
Red Marrow	3.0	0.30
Heart Wall	20	2.0
Liver	5.8	0.58
Bone Surfaces	4.8	0.48

mGY = milligray; rads = unit of absorbed radiation dose

*Assumes non-resting state and biological half-life for all organs and whole body of 63.7 hours. The peak percent dose for heart chambers is 15.5%, for liver is 5.57%, spleen is 4.07% and for remainder of body is 74.8%. Assumes patient voids at 2.0 hour intervals.

Method of Administration
The Instructions for Preparation must be carefully followed for preparing Technetium Tc 99m-Labelled Red Blood Cells using Ultratag RBC.

Parenteral products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Aseptic procedures and a shielded syringe should be employed in preparing and withdrawing doses for administration to patients. The user should wear waterproof gloves during the administration procedure.

[2] Dose estimates based on Phase I human biodistribution data generated at Brookhaven National Laboratories. Dose estimates were calculated at Oak Ridge Associated Universities, Oak Ridge, Tennessee.

It is recommended that the labelled red blood cells be administered within 30 minutes of preparation or as soon as possible thereafter.

Procedure for the Preparation of Technetium Tc 99m-Labelled Red Blood Cells

1. Collect patient's blood sample (1.0 to 3.0 mL) using heparin or Anticoagulant Citrate Dextrose Solution (ACD) as an anticoagulant. The amount of ACD should not exceed 0.15 mL of ACD per mL of blood. The recommended amount of heparin is 10 to15 units per mL of blood. DO NOT USE EDTA OR OXALATE AS AN ANTICOAGULANT.
2. Using a large-bore (19 to 21 gauge) needle, transfer 1.0 to 3.0 mL of anticoagulated whole blood to the Reaction Vial and gently mix to dissolve the lyophilised material. Allow to react for five minutes.
3. Add contents of Syringe I, mix by gently inverting four to five times.
4. Add the contents of Syringe II to the Reaction Vial. Mix by gently inverting four to five times.
5. Place the vial in a lead shield fitted with a lead cap and having a minimum wall thickness of 3mm. Add 370 to 3700 MBq (10 to 100 mCi) Sodium Pertechnetate Tc 99m (in a volume of up to 3 mL) to the Reaction Vial. The avoidance of long Technetium Tc 99m in-growth times and the use of fresh Sodium Pertechnetate Tc 99m generator eluate is recommended.
6. Mix by gently inverting Reaction Vial four to five times. Allow to react for 20 minutes with occasional mixing.
7. Technetium Tc 99m-Labelled Red Blood Cells should be injected within 30 minutes of preparation or as soon as possible thereafter.
8. If desired, assay labelling efficiency immediately prior to injection. Typical labelling efficiency is greater than 95%.
9. Mix gently prior to withdrawal of patient dose. Aseptically transfer the Technetium Tc 99m- Labelled Red Blood Cells to a syringe for administration to the patient. Use largest bore needle compatible with patient administration to prevent hemolysis.
10. Assay the Technetium Tc 99m-Labelled Red Blood Cell patient dose in a suitable calibrator and complete the radioassay information label. Affix the radio assay information label to the shield.

Note 1: The kit does not contain an anticoagulant. Therefore, a syringe or vacutainer™ tube treated with ACD or heparin must be used for drawing the patient's blood. The amount of ACD should not exceed 0.15 mL of ACD per mL of blood. The recommended amount of heparin is 10 to 15 units per mL of blood. Improperly anticoagulated blood will be unsuitable for reinjection.

Note 2: If desired, the labelling yield determination can be carried out as follows: Transfer 0.2 mL of the Technetium Tc 99m-Labelled Red Blood Cells to a centrifuge tube containing 2 mL of 0.9% NaCl. Centrifuge for five minutes and carefully pipet off the diluted plasma. Measure the radioactivity in the plasma and red blood cells separately in a suitable counter.

Calculate labelling efficiency as follows:

$$\% \text{ RBC Labelling} = \frac{\text{Activity RBC} \times 100}{\text{Activity RBC} + \text{Activity Plasma}}$$

4.3 CONTRAINDICATIONS

None known.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The components of the kit are sterile and non-pyrogenic. It is essential that the user follow the directions carefully and adhere to strict aseptic procedures during preparation.

The contents of the kit are intended only for use in the preparation of Technetium Tc 99m-Labelled Red Blood Cells and are NOT to be administered directly to the patient.

The contents of this kit are not radioactive. After Sodium Pertechnetate Tc 99m is added, however, adequate shielding of the final preparation must be maintained.

Technetium Tc 99m-Labelled Red Blood Cells must be handled with care to ensure minimum radiation exposure to the patient, consistent with proper patient management, and to ensure minimum radiation exposure to occupational workers.

The labelled red blood cells must be reinjected only into the patient from whom the blood was drawn.

Nuclear medicine procedures involving withdrawal and reinjection of blood have the potential for transmission of blood borne pathogens. Procedures should be implemented to avoid administration errors and viral contamination of personnel during blood product labelling. A system of checks similar to the ones used for administering blood transfusions should be routine.

It is recommended that the labelled red blood cells be administered within 30 minutes of preparation or as soon as possible thereafter. A small study showed that Technetium Tc 99m-Labelled Red Blood Cells prepared with Ultratag RBC have equivalent *in vivo* labelling efficiency when administered both immediately after preparation (5 patients studied) and at 6 hours after preparation (6 patients studied) with a 24-hour labelling efficiency averaging 97% for both groups.

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorised to license the use of radionuclides.

Use in the elderly
There is no special safety or dosage information available for use in the elderly.

Paediatric use
Safety and efficacy in paediatric patients have not been established.

Effects on laboratory test
This information is not available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clinical trials were conducted with a variety of prescription and non-prescription medications and showed no significant effect on the *in vitro* labelling efficiency of Ultratag RBC. Unlike stannous pyrophosphate red blood cell kits, heparinised patients (11) showed minimal interference with Ultratag RBC labelling efficiency (95% with heparin, 97% without heparin).

4.6 FERTILITY, PREGNACY AND LACTATION

Effects on fertility
This information is not available.

Use in pregnancy
Animal reproduction studies have not been conducted with Technetium Tc 99m-Labelled Red Blood Cells. It is also not known whether this medicine can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m-Labelled Red Blood Cells should be administered to a pregnant woman only if clearly needed. Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.

Use in lactation
Technetium Tc 99m is excreted in human milk during lactation, therefore, formula feedings should be substituted for breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects on ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

None known.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefits-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.giv.au/reporting-problems.

4.9 OVERDOSE

In the event of the accidental administration of an overdose of the radiopharmaceutical very little supportive treatment can be undertaken since its elimination is entirely dependent on the normal haemolytic process. Forced diuresis and frequent bladder voiding are recommended in the case of overdose with Tc 99m Pertechnetate.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
No data available.

General
In vitro Tc 99m red blood cell labelling is accomplished by adding 1.0 to 3.0 milliliters of autologous whole blood, anticoagulated with heparin or Anticoagulant Citrate Dextrose Solution (ACD), to the Reaction Vial. A portion of the stannous ion in the Reaction Vial diffuses across the red blood cell membrane and accumulates intracellularly. The *in vitro* Tc 99m red blood cell labelling efficiency can decrease in the presence of excess ACD. Excess ACD apparently impairs the diffusion of stannous ion across the red blood cell membrane. Therefore, the ACD concentration used for blood collection should not exceed 0.15 mL ACD per mL of blood. Sodium hypochlorite is then added to the Reaction Vial to oxidise the extra cellular

stannous ion. Since the hypochlorite does not cross the red blood cell membrane, the oxidation of stannous ion is selective for the extracellular tin. A citric acid, sodium citrate and dextrose solution is then added to the Reaction Vial to sequester any residual extracellular stannous ion, rendering it more readily available for oxidation by sodium hypochlorite.

Radioactive labelling of the red blood cells is completed by addition of Sodium Pertechnetate Tc 99m to the oxidised Reaction Vial. The Pertechnetate Tc 99m diffuses across the red blood cell membrane and is reduced by the intracellular stannous ion. The reduced Technetium Tc 99m cannot diffuse out of the red blood cell. The red blood cell labelling is essentially complete within 20 minutes of Sodium Pertechnetate Tc 99m addition to the Reaction Vial. Red blood cell labelling efficiency of ≥ 95% is typically obtained using this *in vitro* labelling procedure. *In vitro* Tc 99m red blood cell labelling efficiency can decrease when excessive amounts of Tc 99m are allowed to accumulate in the Sodium Pertechnetate Tc 99m generator eluate; in this situation, efficiency decreases even further if excess (i.e. >0.15 mL per mL of blood) ACD buffer is used. Therefore, long Tc 99m in-growth times are to be avoided; the use of fresh (≤ 24 hour in-growth time) Sodium Pertechnetate Tc 99m generator eluate is recommended. After the labelling procedure is completed, the Technetium Tc 99m-Labelled Red Blood Cells are then reinjected intravenously into the patient for gamma scintigraphic imaging.

Clinical trials
No data available.

5.2 PHARMACOKINETIC PROPERTIES

Distribution
Following intravenous injection, the Technetium Tc 99m-Labelled Red Blood Cells distribute within the blood pool with an estimated volume of distribution of approximately 5.6% of body weight. The Technetium Tc 99m is well retained in the blood pool with an estimated biological half-life of approximately 29 hours. Of the total Technetium Tc 99m retained in the whole blood pool 24 hours after administration, 95% remains bound to the red blood cells.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No long term animal studies have been performed to evaluate carcinogenic or mutagenic potential or to determine the effects on male or female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Reaction Vial:
- glucose
- sodium citrate dihydrate

Syringe I:
- sodium hypochlorite
- water for injections

Syringe II:
- citric acid monohydrate

- glucose
- sodium citrate dihydrate
- water for injections

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Before reconstitution: 15 months from date of manufacture.

After reconstitution: Inject within 30 minutes of preparation where possible. Use within 6 hours of preparation.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before reconstitution:

Kit:

Stored below 25°C. Protect from light.

Do not freeze.

Reaction Vial:

Stored below 25°C. Do not freeze

Syringe I:

Stored below 25°C. Protect from light.

Do not freeze.

Syringe II:

Stored below 25°C. Do not freeze.

After reconstitution:

Stored below 25°C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack contains 5 kits.

Each kit contains:

- 1x reaction glass vial;
- 1x glass syringe I;
- 1x glass syringe II.

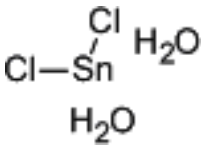
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Stannous chloride dihydrate has the following structural formula:



CAS number

CAS number for stannous chloride dihydrate: 10025-69-1.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled. Not considered by the committee.

8 SPONSOR

Landauer Radiopharmaceuticals Pty Ltd
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Parramatta NSW 2150
Australia
Contact number: (02) 8651 4000

9 DATE OF FIRST APPROVAL

2 February 1994

10 DATE OF REVISION

16 January 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Adopted new TGA approved PI form throughout the document with no change to previously approved TGA text. New text added were necessary to comply with the new PI form.