LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

26 February 2020

Summary of product characteristics

for

Ultratag RBC, kit for radiopharmaceutical preparation

1. NAME OF THE MEDICINAL PRODUCT

Ultratag RBC

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A 10 ml Reaction vial containing (per vial):

Stannous chloride dihydrate: 96 µg maximum
Sodium citrate dihydrate: 3.64 mg
Dextrose anhydrous: 5.50 mg

The contents of the vial are stored under argon.

Syringe I contains:
Sodium hypochlorite: 0.6 mg
Water for injection q.s.: 0.6 ml

Syringe II contains:
Citric acid monohydrate: 8.7 mg
Sodium citrate dehydrate: 32.5 mg
Dextrose anhydrous: 12.0 mg
Water for injection q.s.: 1.0 ml

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation, consisting of three separate non-radioactive components:
Reaction vial: Powder for solution for injection
Syringe I: Concentrate for solution for injection
Syringe II: Concentrate for solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

A In-vivo or in-vivo/in-vitro red blood cell labelling for blood pool scintigraphy. Major indications are:
- Angiocardioscintigraphy for:
  - Evaluation of ventricular ejection fraction,
  - Evaluation of global and regional cardiac wall motion,
  - Myocardial phase imaging.
- Organ perfusion and vascular abnormalities imaging.
- Diagnosis and localisation of occult gastro-intestinal bleeding.

B Determination of blood volume.

C Spleen scintigraphy.

4.2 Posology and method of administration

The individual components of the Ultratag RBC kit are not intended for direct injection into patient. Their intended use is for the in-vitro preparation of Tc-99m labelled blood samples. Only the labelled Tc-99m red blood cells (RBC) are injected.

Administration is by intravenous injection.

The instructions for the preparation of the Technetium Tc 99m-labelled red blood cells using Ultratag RBC must be carefully followed.

A Blood pool scintigraphy
The suggested activity administered by single injection is 370-740 MBq for a patient of 70 kg.

B Determination of blood volume
The average activity administered by single injection after in-vitro labelling is 3 MBq (1-5 MBq).

C Spleen scintigraphy
The average activity administered by single injection for in-vitro labelling of denatured erythrocytes is 50 MBq (20-70 MBq).

Paediatric doses

The activity for children may be calculated from the recommended range of adult activity and adjusted according to body weight or surface area. However, the Paediatric Task Group of EANM recommends calculating the administered activity from the body weight according to the following table.

Fraction of adult dose

3 kg = 0.10	4 kg = 0.14	6 kg = 0.19	8 kg = 0.23	10 kg = 0.27
12 kg = 0.32	14 kg = 0.36	16 kg = 0.40	18 kg = 0.44	20 kg = 0.46
22 kg = 0.50	24 kg = 0.53	26 kg = 0.56	28 kg = 0.58	30 kg = 0.62
32 kg = 0.65	34 kg = 0.68	36 kg = 0.71	38 kg = 0.73	40 kg = 0.76
42 kg = 0.78	44 kg = 0.80	46 kg = 0.82	48 kg = 0.85	50 kg = 0.88
52-54 kg = 0.90	56-58 kg = 0.92	60-62 kg = 0.96	64-66 kg = 0.98	68 kg = 0.99

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

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients

4.4 Special warnings and precautions for use

It is recommended that *In vivo* (^{99m}Tc) RBC labelling be performed prior to administration of iodinated contrast media. Otherwise, labelling efficiency will be adversely affected.

In infants and children, a particularly careful assessment must be made of the diagnostic value, necessity for and risks of the procedure.

4.5 Interactions with other medicinal products and other forms of interactions

Reduction in red blood cell labelling yield has been reported with heparin, tin overload, aluminium, prazosin, methyldopa, hydralazin, digitalic related compounds, quinidine, β-adrenergic blockers (e.g. propanolol) calcium channel blockers (e.g. verapamil, nifedipine), nitrates (e.g. nitroglycerin), anthracycline antibiotic, iodinated contrast agents and Teflon catheter (the Sn^{++} can react with the catheter).

4.6 Pregnancy and lactation

Pregnancy

Only imperative investigations should be carried out during pregnancy, when the likely benefit exceeds the risk incurred by the mother and the foetus.
Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus.

Administration of 740 MBq results in an absorbed dose to the uterus of 3.4 mGy
Doses above 0.5 mGy should be regarded as a potential risk to the foetus.

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.

Lactation

If administration is considered necessary, breast feeding should be interrupted and the expressed feeds discarded. Breast feeding can be restarted about 12 hours post injection or when the level of radioactivity in milk will not result in a radiation dose greater than 1mSv to the child.
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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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.

Congenital, familial and genetic disorders Frequency not known (cannot be estimated from the available data)	Hereditary defects.
Neoplasms benign, malignant and unspecified (including cysts and polyps) Frequency not known (cannot be estimated from the available data)	Cancer induction.
Immune system disorders Frequency not known (cannot be estimated from the available data)	Allergic and anaphylactoid reactions.

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 low frequency because of the low radiation doses incurred.
For most diagnostic investigations using a nuclear medicine procedure effective dose is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

Allergic and anaphylactoid reactions may occur after use of Ultratag RBC.

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 pro-duct. 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

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 dependant on the normal haemolytic process.
Forced diuresis and frequent bladder voiding are recommended in the case of overdosage with sodium (^{99m}Tc) pertechnetate

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic properties

V09AG06 - Diagnostic radiopharmaceuticals cardiovascular system
(^{99m}Tc) Technetium (^{99m}Tc) compounds.

In vitro Tc-99m red blood cell labelling is accomplished by adding 1.0 to 3.0 ml of whole blood, anticoagulated with heparin or 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. A solution of sodium hypochlorite is then added to the Reaction Vial to oxidise the extracellular stannous ion. Since the hypochlorite does not cross the red blood cell membrane, the oxidation is limited to the extracellular stannous ions. 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, and to reduce the remaining amount of hypochlorite.

Radioactive labelling of the red blood cells is completed by addition of sodium pertechnetate Tc-99m to the oxidation 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. The technetium Tc-99m labelled red blood cells are then reinjected intravenously into the patient for gamma scintigraphy imaging.

At doses used for diagnostic procedures, none of the kit components, sodium (^{99m}Tc) pertechnetate, or labelled Red Blood Cells appears to exert any pharmacodynamic effects

5.2 Pharmacokinetic properties

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 bodyweight. The technetium Tc-99m is well retained in the blood pool with an estimated 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. Approximately 25 % of the injected dose is excreted in the urine in the first 24 hours.

5.3 Preclinical safety data

There are no preclinical safety data specific to technetium labelled erythrocytes. The toxicity of pertechnetate ion and stannous salts has been studied and reported in literature. Systemic toxic effects are only observed at relatively high parenteral doses, giving a safety ratio of at least 150. Repeated dose toxicity studies in rats with 50-100 times human dose do not cause macroscopic or microscopic alterations. Stannous salts are reported to have a weak potential for mutagenicity. There are no studies describing possible effects on reproduction or tumour incidence.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The different components of the kit contain following products:
Stannous chloride, dextrose, sodium citrate, sodium hypochlorite.
Hydrochloric acid and sodium hydroxide may be used for pH adjustment.
The technetium is generally available as sodium pertechnetate in saline solution.

6.2 Incompatibilities

None known to date.

6.3 Shelf life

15 months.
Consult the expiry date on the outer package.
The technetium Tc-99m labelled red blood cells using the Ultratag RBC are stable for at least 6 hours.

6.4 Special precautions for storage

Store below 25 °C.
Syringe I should be protected from light if not stored in the kit tray.
Store the labelled cells below 25 °C.

Storage should be in accordance with national regulations for radioactive material.

6.5 Nature and contents of container

Each unit dose kit consists of 3 separate non radio-active components:

- One 10 ml **Reaction vial**, Type I glass Ph. Eur. with butylrubber stopper (Ph. Eur.) and aluminium crimp cap and plastic flip-off.
- One 2.25 ml Type I glass Ph. Eur. pre-filled syringe with Type I Ph. Eur. butylrubber plunger with flurotec coating, called **Syringe I**.
- One 2.25 ml Type I glass Ph. Eur. with Type I ph. Eur. butylrubber plunger pre-filled syringe, called **Syringe II**.

These 3 items are packaged together in a closed plastic unit dose tray along with 2 plastic syringe plunger rods, 2 disposable hypodermic needles and labelling.

The product is available in a carton box containing 5 unit dose trays.

6.6 Special precautions for disposal and other handling

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Therefore, radiation protection precautions in accordance with national regulations must 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
The Netherlands

8. MARKETING AUTHORISATION NUMBER

DK R 22

9. DATE OF FIRST AUTHORISATION

20 May 1999

10. DATE OF REVISION OF THE TEXT

26. February 2020

11. DOSIMETRY

Technetium (^{99m}Tc) decays with the emission of gamma radiation with an energy of 140 keV and a half-life of 6 hours to technetium (^{99}Tc) which can be regarded as quasi stable. The radiation doses absorbed by a patient weighing 70 kg, after intravenous injection of ^{99m}Tc-labelled erythrocytes (ICRP 80 -1999) and ^{99m}Tc-labelled denatured erythrocytes (ICRP 53 – 1988), are reported hereafter.

^{99m}Tc-labelled erythrocytes (ICRP 80 – 1999)

Absorbed dose per unit activity administered (mGy/MBq)

Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	-03	-02	02	-02	-02
Bladder	8.5E-03	1.1E-02	1.4E-02	1.7E-02	3.1E-02
Bone surfaces	7.4E-03	1.2E-02	1.9E-02	3.6E-02	7.4E-02
Brain	3.6E-03	4.6E-03	7.5E-03	1.2E-02	2.2E-02
Breast	3.5E-03	4.1E-03	7.0E-03	1.1E-02	1.9E-02
Gall bladder	6.5E-03	8.1E-03	1.3E-02	2.0E-02	3.0E-02
GI-tract					
Stomach	4.6E-03	5.9E-03	9.7E-03	1.4E-02	2.5E-02
SI	3.9E-03	4.9E-03	7.8E-03	1.2E-02	2.1E-02
Colon	3.7E-03	4.8E-03	7.5E-03	1.2E-02	2.0E-02
ULI	4.0E-03	5.1E-03	8.0E-03	1.3E-02	2.2E-02
LLI	3.4E-03	4.4E-03	6.9E-03	1.0E-02	1.8E-02
Heart	2.3E-02	2.9E-02	4.3E-02	6.6E-02	1.1E-01
Kidneys	1.8E-02	2.2E-03	3.6E-02	5.7E-02	1.1E-01
Liver	1.3E-02	1.7E-02	2.6E-02	4.0E-02	7.2E-02
Lungs	1.8E-02	2.2E-02	3.5E-02	5.6E-02	1.1E-01
Muscles	3.3E-03	4.0E-03	6.1E-03	9.4E-03	1.7E-02
Oesophagus	6.1E-03	7.0E-03	9.8E-03	1.5E-02	2.3E-02
Ovaries	3.7E-03	4.8E-03	7.0E-03	1.1E-02	1.9E-02
Pancreas	6.6E-03	8.1E-03	1.3E-02	1.9E-02	3.3E-02
Red marrow	6.1E-03	7.6E-03	1.2E-02	2.0E-02	3.7E-02
Skin	2.0E-03	2.4E-03	3.8E-03	6.2E-03	1.2E-02
Spleen	1.4E-02	1.7E-02	2.7E-02	4.3E-02	8.1E-02
Testes	2.3E-03	3.0E-03	4.4E-03	6.9E-03	1.3E-02

Thymus	6.1E-03	7.0E-03	9.8E-03	1.5E-02	2.3E-02
Thyroid	5.7E-03	7.1E-03	1.2E-02	1.9E-02	3.6E-02
Uterus	3.9E-03	4.9E-03	7.4E-03	1.1E-02	1.9E-02
Remaining organs	3.5E-03	4.5E-03	7.3E-03	1.3E-02	2.3E-02
Effective dose (mSv/MBq)	**7.0E-03**	**8.9E-03**	**1.4E-02**	**2.1E-02**	**3.9E-02**

For blood pool scintigraphy the effective dose equivalent resulting from an administered dose of 740 MBq is 6.3 mSv (per 70 kg individual) and the typical radiation dose to the critical organ (heart) is 17 mGy.

For blood volume determination the effective dose equivalent resulting from an administered activity of 5 MBq is 0.05 mSv (per 70 kg individual).

^{99m}Tc-labelled denatured erythrocytes (ICRP 53 – 1988):

Absorbed dose per unit activity administered (mGy/MBq)

Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	1.3E-02	1.8E-02	2.7E-02	3.8E-02	6.3E-02
Bladder wall	7.5E-04	1.1E-03	2.1E-03	3.8E-03	7.3E-03
Bone Surfaces	3.1E-03	4.1E-03	6.1E-03	9.5E-03	1.9E-02
Breast	2.1E-03	2.1E-03	4.1E-03	6.8E-03	1.0E-02
GI-tract					
*Stomach wall	1.9E-02	2.1E-02	3.0E-02	4.0E-02	5.8E-02
Small intestine	3.7E-03	4.6E-03	7.7E-03	1.3E-02	2.2E-02
Upper large intest	4.0E-03	4.9E-03	8.5E-03	1.4E-02	2.3E-02
Lower large intest	1.7E-03	2.3E-03	4.3E-03	6.9E-03	1.3E-02
Heart	6.0E-03	7.3E-03	1.1E-02	1.6E-02	2.6E-02
*Kidneys	1.8E-02	2.2E-02	3.2E-02	4.6E-02	7.0E-02
*Liver	1.8E-02	2.3E-02	3.4E-02	4.9E-02	8.7E-02
Lungs	5.7E-03	7.5E-03	1.1E-02	1.7E-02	2.8E-02
Ovaries	1.4E-03	2.2E-03	3.9E-03	7.0E-03	1.2E-02
*Pancreas	3.6E-02	4.0E-02	5.7E-02	7.8E-02	1.2E-01
Red marrow	4.3E-03	6.0E-03	8.4E-03	1.1E-02	1.7E-02
*Spleen	5.6E-01	7.8E-01	1.2E+00	1.8E+00	3.2E+00
Testes	4.7E-04	5.9E-04	1.1E-03	1.7E-03	4.1E-03
Thyroid	6.3E-04	1.0E-03	1.8E-03	3.2E-03	6.6E-03
Uterus	1.4E-03	1.8E-03	3.6E-03	5.9E-03	1.1E-02
Other tissue	3.3E-03	4.1E-03	5.8E-03	8.7E-03	1.5E-02
Effective Dose Equivalent, mSv/MBq	**4.1E-02**	**5.6E-02**	**8.4E-02**	**1.3E-01**	**2.2E-01**

Effective dose (ICRP 80 – 1999): 1.9E-02

For spleen scintigraphy the effective dose equivalent resulting from an administered activity of 70 MBq is 2.9 mSv (per 70 kg individual) and the typical radiation dose to the critical organ (spleen) is 39 mGy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Instructions for labelling

Instructions for the Preparation of Technetium Tc99m-labeled Red Blood Cells Using Ultratag RBC.

Blood collection

1. Connect a thick needle (19 – 21 G) to a 5 ml syringe and flush needle and syringe with anticoagulant (use only heparin or ACD solutions and do not use EDTA or oxalate as an anticoagulant).
   I Heparin: 10 – 15 units/ml of blood
   II ACD solution: 0.15 ml ACD/ml of blood
2. Take a 4 ml blood sample from the patient

Preparation

1. Aseptically transfer 1.0 to 3.0 ml of the anticoagulated whole blood to the 10 ml capacity reaction vial and gently mix to dissolve the lyophilised material.
2. Allow reacting for five minutes.
3. Assemble meanwhile the two buffer syringes from the Ultratag RBC kit and prepare a 3 ml syringe with 370 – 740 MBq (in a volume of up to 3 ml) of Sodium pertechnetate (^{99m}Tc) Injection, Ph.Eur.
4. Gently mix the vial once more.
5. Add contents of Syringe I (Sodium Hypochlorite solution), mix by gently inverting four to five times.
6. Add the contents of Syringe II (Citric acid, Sodium citrate solution) to the reaction vial. Mix by gently inverting four to five times.
7. Place the reaction vial in a lead shield fitted with a lead cap and having a minimum wall thickness of 4 mm.
8. Add 370 to 740 MBq (10 to 20 mCi) Sodium pertechnetate ^{99m}Tc Injection Ph.Eur. (in a volume of up to 3 ml) to the reaction vial.
9. Mix by gently inverting reaction vial four to five times. Allow to react for 20 minutes with occasional mixing (5 – 7 minutes interval).
10. Technetium Tc99m-labeled red blood cells should be used within 6 hours, preferably earlier.
11. If desired, assay labelling efficiency immediately prior to injection. Typical labelling efficiency is greater than 95 %.

Assay labelling yield

1. Prepare during the 20 minutes incubation time a 10 ml capacity syringe and a insulin syringe with (20G) thick needles, flush them with an isotonic saline solution.
2. Select 3 centrifuge tubes with cap and label them respectively RBC, SN (supernatant) and ISBAL (isotonic saline balance).
3. Fill two tubes with isotonic saline solution, 2 ml in tube RBC and 2.3 ml in tube ISBAL
4. After 20 minute's incubation time: transfer with the insulin syringe 0.3 ml of the radiolabelled red blood cells into the centrifuge tube RBC. Close the tube with the cap and mix thoroughly but careful.
5. Centrifuge tubes RBC and ISBAL for 5 minutes (at 3000 rpm).
6. Carefully pipet off (with a flushed 3 ml syringe containing a lumbar needle) the diluted plasma from the RBC labelled tube and transfer to the tube labelled SN.

Note:
Prevent that blood cells are introduced in the SN tube; a residue of 1 mm supernatant is acceptable.

7. Fill the 3 ml syringe (lumbar needle) with 1 ml of isotonic saline and add this to the SN tube.

8. Close both tubes and measure the radioactivity in the plasma and the red blood cells separately in a suitable counter (with low background activity).

Calculate labelling efficiency as follows:

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

Administration

1. Mix gently prior to withdrawal of patient dose. Aseptically transfer the technetium 99mTc-labeled red blood cells to a syringe (prerinsed with saline solution) for administration to the patient. Use largest bore needle compatible with patient administration to prevent hemolysis.
2. Assay the Tc99m-labeled red blood cell patient dose in a suitable calibrator and complete the radio-assay information label. Affix the radio-assay information label to the shield.

Note:
ALWAYS MAKE SURE THAT THE RADIOLABELLED BLOOD IS REINJECTED INTO THE SAME PATIENT.

The kit does not contain an anticoagulant. Therefore, a syringe or vacutainer treated with ACD or heparin must be used for drawing the patient's blood. Improperly anticoagulated blood will be unsuitable for reinjection.

A lead shield fitted with a lead cap and having a minimum wall thickness of 3 to 4 mm must be used for the reaction vial. A lead shielded syringe must be used for the transfer of labelled RBC and the administration to the patient. The syringe must be equipped with a large bore needle compatible with patient administration to prevent haemolysis.

Any unused product or waste material should be disposed of in accordance with local requirements.