Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mediam Stannous Agent 4 milligrams/6.8 milligrams kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Stannous fluoride4.0mg/vial

Sodium medronate (MDP)[methylene diphosphonic acid also known as medronic acid (MDP) sodium salt], 6.8mg/vial (equivalent to 5.4mg medronic acid/vial)

Mediam Stannous Agent is reconstituted with sodium chloride injection (not included in this kit) for the labelling of red blood cells with technetium-99m.

The product before reconstitution contains:

- Sodium: 1.42 mg/vial. This needs to be taken into consideration for patients on a controlled sodium diet.

Technetium-99m decays with the emission of gamma radiation with an energy of 140 keV and a half life of 6 hours to technetium-99 which can be regarded as quasi stable.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
White to off-white freeze dried powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

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

4.2 Posology and method of administration

Administration is by intravenous injection.

Red blood cell (RBC) labelling methods

The stannous MDP complex (non radioactive substance) is first reconstituted with isotonic sodium chloride solution for injection.

In vivo method

Injection of the stannous MDP complex and consecutive injection of sodium [^{99m}Tc] pertechnetate 20-40 minutes later.

Modified *in vivo* method (*in vivo/in vitro*)

Injection of the reconstituted solution of the stannous MDP complex for *in vivo* "stannous loading" of RBC.

In vitro RBC labelling with sodium pertechnetate [^{99m}Tc] after withdrawal of a blood sample.

Reinjection of the labelled red blood cells:

Following reconstitution of the lyophilised product, the recommended volume of stannous MDP complex to be administered to adults and the elderly is 0.03ml/kg body weight. In children a dose calculated with reference to the body weight of the child should be administered.

Subsequent to the administration of the stannous-MDP complex, either Sodium Pertechnetate (^{99m}Tc) Injection (*in vivo* method) or ^{99m}Tc-labelled red blood cells (*in vivo/in vitro method*) is given at the level of 740-925MBq in adults and the elderly.

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 calculation of the administered activity from the body weight according to the following table.

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

(Paediatric Task Group, European Association of Nuclear Medicine)
In very young children (up to 1 year) a minimum dose of 80MBq is necessary in order to obtain images of sufficient quality.

Because of the long lasting fixation of stannous salts on red blood cells, it is recommended not to repeat the procedure within 3 months.

4.3 Contraindications

Hypersensitivity to the active substance(s) or 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.
This radiopharmaceutical may be received, used and administered only by authorised persons in hospitals. Its receipt, storage, use, transfer and disposal are subject to the regulations and the appropriate licences of the local competent official organizations.
In infants and children, a particularly careful assessment must be made of the diagnostic value, necessity for and risks of the procedure.

4.5 Interaction 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 Fertility, pregnancy and lactation

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.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy, when the likely benefit exceeds the risk incurred by the mother and the foetus. Administration of 925MBq ^{99m}Tc-labelled RBCs results in an absorbed dose to the uterus of 4.3mGy. Doses above 0.5mGy should be regarded as a potential risk to the foetus.

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. 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.

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.

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 the radiation dose (EDE) is less than 20mSv. Higher doses may be justified in some clinical circumstances.

Occasionally, hypersensitivity reactions may occur following intravenous administration of medronate. Cases of local rash or generalised rash with itching and dermal irritation have been reported. Onset of the reaction is commonly several hours post-injection and it may last up to 48 hours. Treatment with a non-sedative histamine H_1 antagonist is helpful.

Other reactions reported include a fall in blood pressure and hypotensive symptoms, nausea, vomiting, cutaneous vasodilatation, headache, malaise, edema in the extremities and arthralgia.

Isolated cases of allergic or vasovagal reactions have been reported after administration of red blood cells labelled with technetium-99m but no specific details have been formally recorded.

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 the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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 overdose with sodium [^{99m}Tc] pertechnetate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code V09G A06

Erythrocytes labelled with a radioisotope are not expected to have any pharmacological activity. The labelling is achieved by an initial injection of a stannous salt to "load" the erythrocytes with a reducing agent so that the subsequent administration of pertechnetate [^{99m}Tc] will result in accumulation of ^{99m}Tc bound to the β-chains of globin in the cells. None of these processes involves sufficient chemical material to produce any pharmacodynamic effects.

5.2 Pharmacokinetic properties

Intravenous injection of stannous salts effects a "stannous loading" of erythrocytes. When sodium [^{99m}Tc] pertechnetate is subsequently injected there is enhanced accumulation and retention of sodium [^{99m}Tc] pertechnetate in the choroid plexus and red blood cells. Under normal circumstances intravenously injected pertechnetate freely diffuses in and out of erythrocytes. However, when they have been preloaded with stannous ion the sodium [^{99m}Tc] pertechnetate is reduced within the cells and becomes bound to the β-chains of the globin. The mechanisms by which sodium [^{99m}Tc] pertechnetate becomes attached to tin primed red blood cells are not clearly understood. However, reducing surface charge decreases the efficiency of labelling with pertechnetate by up to 20%. Moreover 20% of injected pertechnetate enters the red cell and binds with a beta chain of globin. The remaining 70-80% of pertechnetate is believed to be in a more intra-cellular pool such as the cytoplasm or on the red cell membrane.
The stannous MDP complex results in a labelling efficiency of 95% five minutes after injection of sodium [^{99m}Tc] pertechnetate. Unbound sodium [^{99m}Tc] pertechnetate is cleared by the kidneys and the amount of radioactivity in the plasma constitutes less than 5% of intravascular radioactivity. The ^{99m}Tc concentration of red cells increases during the first 10-15 minutes after injection and then remains level for several hours. The percentage of injected pertechnetate appearing in the urine during the first two hours of injection amounts to about 5%.

5.3 Preclinical safety data

There are no preclinical safety data specific to technetium labelled erythrocytes. The technetium bound to erythrocyte protein is cleared very slowly, presumably following the cellular life-span.

The toxicity of pertechnetate ion and stannous salts has been studied and reported in the literature. General toxic effects are only observed at relatively high parenteral doses of all the salts involved, giving a safety margin based on mg/kg of at least 150.

Repeated administration of very high doses of diphosphonates can cause demineralization disorders.

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

Not applicable

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

18 months from the date of manufacture.

The reconstituted product should be stored below 25°C. Do not freeze. The reconstituted injection should be used within 2 hours of removing the first patient dose and within 6 hours of preparation.

6.4 Special precautions for storage

Store below 25°C.
Storage should be in accordance with national regulations for radioactive material.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

10ml, Type 1, Ph.Eur., clear, colourless, borosilicate glass vial sealed with a chlorobutyl rubber closure and oversealed with an aluminium overseal with a yellow flip off cap.

6.6 Special precautions for disposal and other handling

Normal safety precautions for handling radioactive materials should be observed. After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via an authorised route.

7 MARKETING AUTHORISATION HOLDER

MEDiAM
21 Avenue de Verdun
59700 Marcq en Baroeul
France

8 MARKETING AUTHORISATION NUMBER

PA1229/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 1999
Date of last renewal: 22 January 2009

10 DATE OF REVISION OF THE TEXT

November 2017

11 DOSIMETRY

Technetium-99m decays with the emission of gamma radiation with an energy of 140 keV and a half life of 6 hours to technetium-99 which can be regarded as quasi stable.

The radiation doses absorbed by a patient weighing 70kg, after intravenous injection of ^{99m}Tc labelled erythrocytes, are reported hereafter (ICRP 80-1988).

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**15 year**	**10 year**	**5 year**	**1 year**
Adrenals	8.7E-03	1.1E-02	1.7E-02	2.7E-02	4.9E-02
Bladder wall	9.2E-03	1.2E-02	1.7E-02	2.5E-02	4.6E-02
Bone surfaces	9.2E-03	1.3E-02	2.3E-02	3.9E-02	7.8E-02
Breast	4.3E-03	4.5E-03	7.2E-03	1.1E-02	1.9E-02
GI-tract					
Stomach wall	4.8E-03	6.1E-03	9.5E-03	1.4E-02	2.4E-02
Small intest	4.4E-03	5.3E-03	8.1E-03	1.2E-02	2.2E-02
ULI wall	4.3E-03	5.5E-03	7.9E-03	1.3E-02	2.1E-02
LLI wall	3.9E-03	5.3E-03	8.0E-03	1.1E-02	2.1E-02
Heart	2.3E-02	2.8E-02	4.1E-03	6.2E-02	1.1E-01
Kidneys	1.0E-02	1.2E-02	1.9E-02	3.0E-02	5.5E-02
Liver	7.5E-03	8.8E-03	1.4E-02	2.1E-02	3.8E-02
Lungs	1.4E-02	1.8E-02	2.9E-02	4.5E-02	8.5E-02
Ovaries	4.2E-03	5.4E-03	7.9E-03	1.2E-02	2.1E-02
Pancreas	6.2E-03	7.5E-03	1.1E-02	1.7E-02	2.9E-02
Red marrow	7.3E-03	8.8E-03	1.3E-02	2.0E-02	3.5E-02
Spleen	1.5E-02	1.8E-02	2.8E-02	4.4E-02	8.4E-02
Testes	2.7E-03	3.7E-03	5.4E-03	8.3E-03	1.5E-02
Thyroid	4.9E-03	7.1E-03	1.2E-02	1.9E-02	3.5E-02
Uterus	4.7E-03	5.7E-03	8.5E-03	1.3E-02	2.2E-02
Other tissue	3.7E-03	4.4E-03	6.4E-03	9.8E-03	1.8E-02
Effective dose equivalent (mSv/MBq)	8.5E-03	1.1E-02	1.6E-02	2.5E-02	4.6E-02

For this product the effective dose equivalent resulting from an administered dose of 925MBq is 7.9mSv (per 70kg individual).

For an administered activity of 925MBq the typical radiation dose to the critical organ (heart) is 21mGy.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

This radiopharmaceutical may 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 local competent official organisations (see section 6.6).

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Normal safety precautions for the handling of radioactive materials should be observed in addition to the use of aseptic technique to maintain sterility of the vial contents.

Method of preparation of the final dosage form for injection

Use aseptic technique throughout

(1) Swab the vial closure with the sanitising swab provided.

(2) Using a 10ml syringe inject 6.0ml sterile, pyrogen free isotonic saline (containing no preservatives) into one of the vials. Before removing the syringe needle, withdraw an equivalent volume of gas from the space above the solution to normalise the pressure in the vial. Shake the vial to ensure complete dissolution of the powder. The preparation is now ready for intravenous injection. Do not introduce air into the vial when removing a patient dose. The reconstituted injection should be used within 2 hours of removing the first patient dose and in any case within 6 hours of reconstitution.

Notes:

(1) Individual patient doses taken from the vial immediately after reconstitution may be stored aseptically in a syringe with a capped needle or blanking tip for periods of up to 6 hours.

(2) The vial should not be reconstituted with eluate from a technetium generator.

Procedure for the in vitro labelling of stannous loaded red blood cells (modified in vivo method)

This method facilitates injection of red cells free from ^{99m}Tc-pertechnetate ion leading to increased target to background ratios. This method also allows labelled red cells to be injected as a bolus for first pass cardiac studies.

Use aseptic technique throughout.

(1) Between 15 and 30 minutes after administration of the reconstituted injection remove 3 to 5ml of patient's blood into heparinised syringe. (A suggested protocol for heparinising the syringe is as follows: wet the syringe with a few drops of heparin (5000 U/ml) and then rinse the syringe with heparin (10 U/ml) in a solution of 0.9% sodium chloride).

(2) Incubate 3ml of this heparinised blood with 1.11 – 1.48 GBq (30-40 mCi) sterile eluate from a technetium-99m generator (Sodium Pertechnetate (^{99m}Tc) Injection) for 10 minutes at 37ºC (or 20 minutes at room temperature) in a closed sterile centrifuge tube.

(3) After incubation add 5 ml saline (sodium chloride injection) and centrifuge for 10 minutes at 500g.

(4) Remove the supernatant and measure the activity as a quality control for sodium [^{99m}Tc] pertechnetate not bound to red cells.

(5) Resuspend the red cells in 0.9% sodium chloride and reinject the patient with 1-1.5 ml blood containing the required activity of technetium-99m.

Imaging is normally commenced a few minutes after injection of the technetium-99m labelled red cells. If first pass cardiac studies are to be performed the technetium is injected as a bolus immediately prior to scintigraphy.

Determination of radiolabelling efficiency

If required, the radiolabelling efficiency of the radiolabelling procedure may be determined by comparing the activity level in the labelled cell suspension with that in the radiolabelling supernatant.

$$\% \text{ labelling efficiency} = \frac{Ac \times 100}{Ac + As}$$

Where Ac is the activity in the labelled cell suspension
As is the activity remaining in the radiolabelling supernatant