AUSTRALIAN PRODUCT INFORMATION

MDP KIT (MEDRONIC ACID) FOR INJECTION

1 NAME OF THE MEDICINE

MDP Kit for preparation of Technetium (^{99m}Tc) Medronate injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 5.00 mg Methylene Diphosphonic Acid (Medronic Acid, equivalent to 6.25 mg of Sodium salt of Methylene Diphosphonic Acid), 0.417 mg Stannous Chloride Dihydrate, 2.0 mg of Ascorbic Acid, Hydrochloric Acid (QS) and Sodium Hydroxide (QS).

Before lyophilisation the pH is adjusted to 6.0 with Sodium Hydroxide or Hydrochloric Acid solutions. The contents the vial is lyophilized and stored under nitrogen.

As supplied the product is sterile and pyrogen free; it contains no antimicrobial preservative.

The product is for diagnostic use only, for intravenous administration after reconstitution with sterile sodium pertechnetate (^{99m}Tc) solution.

For the full list of excipients, see Section 6.1 List of Excipients.

Physical Characteristics of ^{99m}Tc
Technetium-99m, with a physical half-life of six hours, decays by isomeric transition to ^{99}Tc. Photons associated with this transition that are useful for detection and imaging studies are listed in Table 1. Decay profile of ^{99m}Tc is given in Table 2.

Table 1: Principal Radiation Emission Data for ^{99m}Tc.

Principal Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	89.1	140.5

Reference: "D A Weber, K F Eckerman, LT Dillman and JC Ryan. MIRD: Radionuclide and Decay Schemes." The society of Nuclear Medicine Inc. New York, 1989.

Table 2: Physical Decay Chart of ^{99m}Tc.

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1.000	7	0.445
1	0.891	8	0.397
2	0.794	9	0.354
3	0.707	10	0.315
4	0.630	11	0.281
5	0.561	12	0.250
6	0.500		

External Radiation
The specific gamma ray constant for ^{99m}Tc is 0.19mGy per MBq^{-h} at 1cm. The first half value thickness of lead (Pb) for ^{99m}Tc is 0.2mm. A range of values for the relative attenuation of the radiation emitted by ^{99m}Tc resulting from the interposition of various thicknesses of lead is given in Table 3.

Table 3: Relative attenuation of radiation emitted by ^{99m}Tc at various Lead (Pb) shield thickness.

Shield Thickness mm Pb	Coefficient of Attenuation
0.95	0.1
1.8	0.01
2.7	0.001
3.6	0.0001

3 PHARMACEUTICAL FORM

- Kit for radiolabelling to produce ^{99m}Tc-medronate radiopharmaceutical preparation.
- Sterile, pyrogen free, freeze dried solid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

^{99m}Tc-medronate may be used as a bone imaging agent to delineate areas of altered osteogenesis.

4.2 DOSE AND METHOD OF ADMINISTRATION

(a) ^{99m}Tc-medronate is prepared for clinical use as follows:

MDP is designed for labelling with technetium-99m (as sodium pertechnetate-^{99m}Tc) obtained from Mo-99 / Tc-99m sterile generators (such as ANSTO's GENTECH® generator or equivalent generators from other manufacturers). The labelling procedure should be performed in a work-station providing protection against ionizing radiation and using aseptic techniques that ensure sterility of the reconstituted injection preparation.

Labelling procedure:

- Place MDP Kit vial containing the lyophilisate in an appropriate radioprotective shield.
- Using a syringe inject (by piercing the rubber stopper) about 5 mL of eluate of sodium pertechnetate ^{99m}Tc (or eluate with desired activity pre-diluted with sterile saline) into freeze-dried MDP Kit vial.
- Using the same syringe relieve excess pressure in the vial by withdrawing volume of gas equivalent to the volume of sodium pertechnetate ^{99m}Tc solution added.
- Shake contents of the vial until complete dissolution of the freeze-dried solid (about 2 minutes). Keep vial in shield all the time. Leave the vial for 15 min.

- The resultant solution is a ready for use as ^{99m}Tc-medronate solution for injection.
- It is recommended that ^{99m}Tc-medronate Injection solution is used within 6 hours after completion of the labelling procedure.

Note:

(i) Using proper shielding, the vial containing the reconstituted solution should be visually inspected to ensure it is free from particulate matter.

(ii) The product should be used as soon as possible after reconstitution.

(b) Recommended activity:

- For radiolabelling of one vial of MDP, 5 mL sodium pertechnetate (^{99m}Tc) solution (eluate from a radionuclide ^{99}Mo/^{99m}Tc generator) with activity of 1100-18500 MBq may be used.

- The activity recommended for bone imaging examination of a single adult patient (70kg) ranges from 370-740 MBq of ^{99m}Tc-medronate.

- Patient dose should be measured by a suitable radioactivity calibrator immediately before administration.

(c) Determination of Radiochemical Purity:

The radiochemical purity should be checked prior to patient administration. It can be measured by Thin Layer Chromatography – using two chromatographic systems according to Ph. Eur. Monograph 0641. Appropriate radiation protection should be practised.

Impurity A: [^{99m}Tc] technetium in colloidal form

(i) TLC silica gel plate: Use silica gel as the coating substance on a glass-fibre sheet.

(ii) Mobile phase: 136 g/L solution of sodium acetate.

(iii) Application: about 2 µL of the examined solution (with radioactivity from 50 MBq/mL to 200 MBq/mL) about 1.5 cm from the bottom of a 1.5 cm x 12 cm chromatographic plate.

(iv) Development: Immediately, until the solvent front moves to about 4/5 of the plate.

(v) Drying: In the air.

(vi) Detection: Suitable detector to determine the distribution of radioactivity.

(vii) Retardation factors:

- Impurity A = 0.0 to 0.1 (Rf value).
- Impurity B and [^{99m}Tc] technetium medronate = 0.9 to 1.0 (Rf value).

Impurity B: [^{99m}Tc] pertechnetate ion

(i) TLC silica gel plate: Use silica gel as the coating substance on a glass-fibre sheet.

(ii) Mobile phase: methyl ethyl ketone.

(iii) Application*:* about 2 µL of the examined solution (with radioactivity from 50 MBq/mL to 200 MBq/mL) about 1.5 cm from the bottom of a 1.5 cm x 12 cm chromatographic plate.

(iv) Development: Immediately, until the solvent front moves to about 4/5 of the plate in about 10 min.

(v) Drying: In the air.

(vi) Detection: Suitable detector to determine the distribution of radioactivity.

(vii) Retardation factors:

- Impurity A and [^{99m}Tc] technetium medronate = 0.0 to 0.1 (Rf value).
- Impurity B = 0.9 to 1.0 (Rf value).

Limit:
[^{99m}Tc] technetium medronate: minimum 95 per cent of the total radioactivity due to technetium-99m.

Calculate the percentage of radioactivity due to [^{99m}Tc] technetium medronate using the following expression:

$100 - (A + B)$

Where,

A = percentage of radioactivity due to impurity A determined in the test for impurity A under Radiochemical purity;

B = percentage of radioactivity due to impurity B determined in the test for impurity B under Radiochemical purity.

Radiation Dosimetry

The absorbed radiation doses to organs and tissues of a patient after intravenous injection of ^{99m}Tc-medronate (^{99m}Tc - labelled phosphates and phosponates) are given in tables 4 and 5 below. The data have been taken from "ICRP publication 128, Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances"; p.214-217.

Table 4: Absorbed dose per unit activity administered (mGy MBq^{-1}) in Patients with normal uptake and excretion / renal function.

Organ	Absorbed dose per unit activity administered (mGy MBq^{-1})				
	Adult	15 years	10 years	5 years	1 year
Adrenals	2.1E_03	2.6E_03	3.8E_03	5 .8E_03	1.1E_02
Bone surfaces	3.4E_02	1.5E_02	2.3E_02	3.8E_02	8.2E_02
Brain	1.7E_03	2.0E_03	2.8E_03	4.2E_03	5.9E_03
Breast	6.9E_04	8.6E_04	1.3E_03	2.1E_03	4.0E_03
Gallbladder wall	1.4E_03	1.8E_03	3.3E_03	4.3E_03	6.5E_03
Gastrointestinal tract -					
Stomach wall	1.2E_03	1.4E_03	2.4E_03	3.6E_03	6.4E_03
Small intestine wall	2.2E_03	2.8E_03	4.3E_03	6.1E_03	9.3E_03
Colon wall	2.7E_03	3.4E_03	5.2E_03	7.2E_03	1.0E_02
(Upper large intestine wall	1.9E_03	2.4E_03	3.8E_03	5.7E_03	8.7E_03)
(Lower large intestine wall	3.8E_03	4.7E_03	7.1E_03	9.2E_03	1.3E_02)
Heart wall	1.2E_03	1.5E_03	2.2E_03	3.3E_03	5.9E_03
Kidneys	7.2E_03	8.7E_03	1.2E_02	1.8E_02	3.1E_02
Liver	1.2E_03	1.6E_03	2.4E_03	3.6E_03	6.4E_03
Lungs	1.2E_03	1.6E_03	2.3E_03	3.5E_03	6.7E_03
Muscles	1.8E_03	2.2E_03	3.3E_03	4.7E_03	7.7E_03
Oesophagus	1.0E_03	1.3E_03	1.9E_03	2.9E_03	5.1E_03
Ovaries	3.6E_03	4.5E_03	6.5E_03	8.6E_03	1.2E_02
Pancreas	1.6E_03	2.0E_03	3.0E_03	4.5E_03	7.9E_03
Red marrow	5.9E_03	5.4E_03	8.8E_03	1.7E_02	3.6E_02
Skin	9.9E_04	1.3E_03	1.9E_03	3.0E_03	5.3E_03
Spleen	1.4E_03	1.8E_03	2.7E_03	4.4E_03	7.7E_03
Testes	2.4E_03	3.3E_03	5.4E_03	7.5E_03	1.0E_02
Thymus	1.0E_03	1.3E_03	1.9E_03	2.9E_03	5.1E_03
Thyroid	1.3E_03	1.5E_03	2.2E_03	3.4E_03	5.4E_03
Urinary bladder wall	4.7E_02	5.9E_02	8.7E_02	1.1E_01	1.3E_01
Uterus	6.2E_03	7.5E_03	1.1E_02	1.4E_02	1.8E_02
Remaining organs	1.9E_03	2.3E_03	3.4E_03	5.0E_03	7.7E_03
Effective dose (mSv MBq^{-1})	4.9E_03	5.7E_03	8.6E_03	1.2E_02	1.8E_02

Reference: "ICRP publication 128, Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances".

Note:
In order to reduce radiation dose to bladder the patient should be encouraged to drink fluids and to void as frequently as possible following the administration of the radiopharmaceutical for a period of four to six hours.

Table 5: Absorbed dose per unit activity administered (mGy MBq^{-1}) in Patients with high bone uptake and/or severely impaired kidney function.

Organ	Absorbed dose per unit activity administered (mGy MBq^{-1})				
	Adult	15 years	10 years	5 years	1 year
Adrenals	4.0E_3	5.0E_3	7.2E_3	1.1E_2	2.1E_2
Bone surfaces	6.5E_2	3.0E_2	4.5E_2	7.4E_2	1.6E_1
Brain	3.7E_3	4.5E_3	6.3E_3	9.6E_3	1.4E_2
Breast	1.7E_3	2.1E_3	3.2E_3	5.0E_3	9.6E_3
Gallbladder wall	2.8E_3	3.6E_3	5.9E_3	8.5E_3	1.3E_2
Gastrointestinal tract -					
Stomach wall	2.5E_3	3.2E_3	5.1E_3	7.3E_3	1.4E_2
Small intestine wall	3.0E_3	3.8E_3	5.6E_3	8.5E_3	1.5E_2
Colon wall	3.0E_3	3.8E_3	5.8E_3	9.1E_3	1.6E_2
(Upper large intestine wall	2.8E_3	3.6E_3	5.3E_3	8.6E_3	1.5E_2)
(Lower large intestine wall	3.3E_3	4.2E_3	6.5E_3	9.8E_3	1.8E_2)
Heart wall	2.9E_3	3.6E_3	5.2E_3	7.7E_3	1.4E_2
Kidneys	2.9E_3	3.7E_3	5.6E_3	8.7E_3	1.6E_2
Liver	2.6E_3	3.3E_3	4.9E_3	7.4E_3	1.4E_2
Lungs	2.9E_3	3.7E_3	5.4E_3	8.1E_3	1.5E_2
Muscles	2.9E_3	3.6E_3	5.3E_3	8.0E_3	1.5E_2
Oesophagus	2.5E_3	3.1E_3	4.5E_3	7.0E_3	1.2E_2
Ovaries	3.2E_3	4.1E_3	5.8E_3	8.8E_3	1.6E_2
Pancreas	3.2E_3	4.0E_3	5.8E_3	8.8E_3	1.6E_2
Red marrow	1.1E_2	1.0E_2	1.7E_2	3.2E_2	7.1E_2
Skin	1.9E_3	2.4E_3	3.7E_3	6.0E_3	1.1E_2
Spleen	2.6E_3	3.4E_3	5.1E_3	8.4E_3	1.5E_2
Testes	2.2E_3	2.7E_3	3.8E_3	6.0E_3	1.1E_2
Thymus	2.5E_3	3.1E_3	4.5E_3	7.0E_3	1.2E_2
Thyroid	3.1E_3	3.7E_3	5.3E_3	8.2E_3	1.4E_2
Urinary bladder wall	2.6E_3	3.5E_3	5.4E_3	7.3E_3	1.5E_2
Uterus	2.9E_3	3.7E_3	5.3E_3	8.1E_3	1.5E_2
Remaining organs	3.0E_3	3.7E_3	5.5E_3	8.6E_3	1.5E_2
Effective dose (mSv MBq^{-1})	4.3E_3	4.5E_3	6.8E_3	1.1E_2	2.2E_2

Reference: "ICRP publication 128, Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances".

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Radiopharmaceuticals should be used only by physicians who are qualified and licensed to handle radioactive materials. Contents of the vial are intended only for use in the preparation of ^{99m}Tc-medronate. They should not be administered directly to the patient. ^{99m}Tc-medronate should be reconstituted within six hours prior to use. Imaging should be carried out between one and four hours after injection.

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.
In patients with renal impairment careful consideration of the indication is required since an increased exposure is possible in these patients.

Dose Handling

Radiation exposure to clinical personnel must be minimised. Care and appropriate safety measures should always be used. The radioactivity of the dose should be checked with a suitable instrument immediately prior to administration.

MDP vial contains no bactericide. Aseptic procedures must be used at all times when handling the product.

Patient Care:

Care should be taken to minimise unwanted radiation exposure to patients, consistent with proper patient management.

In order to reduce radiation dose to the bladder, the patient should be encouraged to drink fluids and to void (empty bladder) as frequently as possible following the administration of the radiopharmaceutical for a period of four to six hours.

Patients with renal impairment

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

Use in the elderly

The activity recommended for a single examination of skeletal system in adult patient ranges from 370 to 740 MBq, however depending on indications other activities may be justifiable. Refer to section "4.2 dose and method of administration" for details.

Paediatric use

Safety and efficacy in children have not been established.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

An increased extraosseous accumulation of the radiotracer is reported in concomitant administration of iron containing compounds, acute administration of diphosphonate, several cytostatic and immunosuppressive drugs, aluminium-containing antacids, X-ray contrast media, antibiotics, anti-inflammatory substances, injections of calcium gluconate, heparin calcium and γ-amino-caproic acid.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Adequate long-term studies have not been performed in animals to determine whether this drug affects fertility, or has teratogenic or mutagenic potential.

Use in pregnancy
It is not known if ^{99m}Tc-medronate can cause foetal harm when administered to a pregnant woman. Technetium (^{99m}Tc) should only be given to a pregnant woman if in the judgement of the treating physician the expected benefits outweigh the potential hazards.

Use in lactation
Technetium (^{99m}Tc) is excreted in human milk. If administered to a nursing mother, formula feeding must be substituted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions have not been reported that are specifically attributable to the use of ^{99m}Tc-medronate. Allergic dermatological manifestations (erythema) have been infrequently reported with other similar agents.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at - *www.tga.gov.au/reporting-problems*.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Upon intravenous injection, skeletal uptake of ^{99m}Tc-medronate appears to be related to bone metabolic activity and to skeletal blood flow. ^{99m}Tc-medronate exhibits a specific affinity for areas of altered osteogenesis.

Localised areas of decreased skeletal accumulation of ^{99m}Tc-medronate may be seen after therapeutic external irradiation. ^{99m}Tc-medronate has been known to accumulate in areas of acute myocardial infarction from one to fourteen days after the initial event.

Clinical trials
No data available at the time of registration.

5.2 PHARMACOKINETIC PROPERTIES

Excretion

During the first 24 hours post injection about 50% of the dose is renally excreted; less than 2% of the dose remains in the vascular system. Blood level dose fall to 3 - 5% of the injected dose by three hours post injection.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity/Carcinogenicity

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Stannous Chloride Dihydrate, BP
Ascorbic Acid, BP
Hydrochloric Acid, BP
Sodium Hydroxide, BP

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except with those as required to achieve therapeutic indications given in Section 4.2 of this Product Information document.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging under this heading.

Note: Reconstituted ^{99m}Tc-medronate should be used within 6 hours of reconstitution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

MDP Kit should be stored between 2-8°C (Refrigerate. Do not freeze).

- The reconstituted ^{99m}Tc-medronate should be stored below 8°C and used within 6 hours of reconstitution.

- During transportation MDP kit can be handled / stored up to 35°C (for no longer than 7 days).

6.5 NATURE AND CONTENTS OF CONTAINER

(i) Primary (vial): The primary container is a labelled 10mL glass vial closed with grey colour rubber stopper and sealed with a red colour aluminium cap.

(ii) Secondary (outer carton): Glass vials are packed in a carton. Each carton box contains: 6 x Labelled vials.

Note: MDP pack contains 6 single dose vials, each vial for use in one patient on one occasion only. Contains no antimicrobial preservative. Each vials is packed under nitrogen.

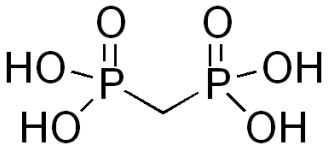
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Disposal of all radioactive wastes should be carried out in accordance with the ARPANSA's "Code for the Disposal of Radioactive Waste by the User - Radiation Protection Series, C-6, September 2018".

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



CAS number: 1984-15-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled.

8 SPONSOR

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Product Code: 20234

Australian Registration Number:
AUST R: 297380

9 DATE OF FIRST APPROVAL

11 December 2017.

10 DATE OF REVISION

15 December 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	- Update to new PI format - Minor editorial updates
2	- Updated: • The contents of the vial to "freeze-dried solid" • The vial seal to "sealed in nitrogen atmosphere"
3	- Included "pharmaceutical form" information
4	- Included / updated: • The reconstitution procedure for 99mTc-medronate (section 4.2- a) • "Recommended activity (section 4.2 (b)" • The "Radiochemical Purity' determination (section 4.2 – c) • The Radiation Dosimetry section for "radiation absorbed dose of ^{99m}Tc-medronate" in tables 4 & 5 as per updated ICRP publication 128 • Contraindications (section 4.3) • Effects on laboratory tests • Interactions with other medicines and other forms of interactions (section 4.5) • Effects on ability to drive and use machines (section 4.7) • Adverse effect (section 4.8) • Overdose (section 4.9)
5	- Included / updated: • Clinical trials (section 5.1). • Preclinical safety data (section 5.3)
6	- Included / updated: • List of excipients (section 6.1) • Incompatibilities (section 6.2) • Shelf-life (section 6.3) • Special precautions for storage (section 6.4) • Nature and contents of container (section 6.5) • Special precautions for disposal (section 6.6) • Physiochemical properties (section 6.7)
7	- Included "medicine schedule (poisons standard)"
8	- Information updated
9	- Included "date of first approval"
10	- Included "date of revision"
N/A	- Included "summary table of changes"