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06.2022

רופא/ה רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלון לרופא בעקבות "אימוץ עלון כלשונו" עבור התכשיר:

FROSTIMAGE/DRAXIMAGE KIT FOR THE PREPARATION OF TC99M (MDP)

חומר פעיל :

Medronic acid 10 mg/vial

התוויה מאושרת:

Bone imaging.

להלן עלון לרופא כפי שאומץ מעלון אסמכתא כלשונו (טקסט מסומן ירוק משמעותו עדכון ,טקסט מסומן צהוב משמעותו החמרה):

SUMMARY OF PRODUCT CHARACTERISTICS

FROSTIMAGE/DRAXIMAGE KIT FOR THE PREPARATION OF TC99M (MDP)

For Intravenous Use,

Solution for Injection containing

Medronic acid 10 mg/vial

1 INDICATIONS

Bone imaging.

Technetium Tc 99m Medronate Injection is a skeletal imaging agent used to demonstrate areas of altered osteogenesis as seen, for example, in metastatic bone disease, Paget's disease, arthritic disease and osteomyelitis.

2 CONTRAINDICATIONS

Technetium Tc 99m Medronate injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

MDP should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

To minimize the contribution of the bladder content to the image, the patient should void immediately before imaging is started.

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

Using proper shielding, parenteral drug products should be inspected for particulate matter and discoloration prior to administration. Do not use if the solution contains particulate matter or is not a clear solution.

4.2 Recommended Dose and Dosage Adjustment

The recommended adult dose of Technetium Tc 99m Medronate injection is 370 MBq to 740 MBq (7.4 MBq/Kg) [10 mCi to 20 mCi (200 mcCi/Kg)] by slow intravenous injection over a period of 30 seconds.

The maximum dose is limited to 10 mg (see 4.7 Instructions for Preparation and Use).

4.3 Reconstitution

Reaction vials containing the sterile, non-pyrogenic, lyophilized powder are reconstituted with 2 to 10 mL of sterile non-pyrogenic sodium pertechnetate Tc 99m to prepare Tc 99m Medronate Injection. The recommended **maximum amount** of Technetium Tc 99m (at the time of elution) to be added to a reaction vial is 18.5 GBq (500 mCi) for MDP (see 11 STORAGE, STABLITY and DISPOSAL).

4.4 Administration

See 4.7 Instructions for Preparation and Use for the preparation of Technetium Tc 99m Medronate injection using the MDP kit.

- Visually inspect the Technetium Tc 99m Medronate injection prepared using the MDP kit is reconstitution for particulate matter or discolouration prior to administration. Do not use or administer if there is evidence of foreign matter or the solution is not clear.
- Measure the patient dose by a radioactivity calibration system immediately prior to administration. Withdrawal for administration must be made aseptically.

4.6 Image Acquisition and Interpretation

Optimal imaging results are obtained 1 to 4 hours after administration. The quality of the image may be affected by specific patient conditions.

4.7 Instructions for Preparation and Use

- Waterproof gloves are to be worn during the preparation and elution processes;
- Aseptic techniques should be employed throughout the preparation and elution processes.

Before reconstituting with an authorized Tc 99m generator, the vials should be inspected for cracks and/or a melted plug or any other indication that the integrity of the vacuum seal has been lost.

The Tc 99m pertechnetate eluate should be less than 2 hours old and should be obtained from a generator which has been eluted within the last 24 hours.

To prepare Technetium Tc 99m Medronate Injection:

1. Remove the protective disc from the reaction vial and swab the closure with an alcohol swab.

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2. Place the vial in a suitable lead vial shield which has a minimum wall thickness of 3 mm (1/8 inch) and which has a fitted lead cap. Obtain 2 to 10 mL of sterile, non-pyrogenic sodium pertechnetate Tc 99m using a shielded syringe. The **maximum amount** of Technetium Tc 99m (at the time of elution) to be added to a reaction vial is 18.5 GBq (500 mCi). Sufficient sodium pertechnetate is to be used for the reconstitution of a reaction vial to ensure that the dose of medronate administered does not exceed 10 mg. Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use.

3. Using a shielded syringe, aseptically add the sodium pertechnetate Tc 99m solution to the reaction vial, while avoiding the build up of excessive pressure in the vial. Pressure build up may be avoided by injecting several millilitres of pertechnetate solution into the reaction vial, then withdrawing several millilitres of nitrogen gas (present to prevent oxidation of the complex) into the syringe. The procedure is repeated as necessary until the entire amount of pertechnetate is added to the vial and normal pressure is established within the vial.

4. Place the lead cap on the vial shield and agitate the shielded vial until the contents are completely dissolved. To ensure maximum radiolabelling, allow the preparation to stand for 5 to 15 minutes at room temperature (15 °C to 30 ºC). Using proper shielding, the reaction vial should be visually inspected to ensure that the solution is clear and free of particulate matter before proceeding; if it is not, the radiopharmaceutical should not be used.

5. Assay the product in a suitable calibrator, record the radioassay information, date and time on the label with radiation warning symbol. Apply the label to the lead vial shield.

6. The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochemical purity should not be less than 90%.

7. Withdrawals for administration must be made aseptically using a sterile needle and syringe. Since the vials contain nitrogen, the vials should not be vented. If repeated withdrawals are made, the replacement of the contents from the vial with air should be minimized.

8. The finished preparation should be discarded 12 hours after reconstitution. While radioactive, it should also be retained in a lead vial shield with the lead cap in place.

Directions for Quality Control

Radiochemical Purity

Chromatographic Methods

The following procedure describes a series of simple steps for running chromatograms. Step 5 describes two methods, one for determining free pertechnetate in a mixture of chelated and reduced technetium and the other for determining reduced technetium in a mixture of chelated technetium and pertechnetate. The TLC procedure requires the following:

Solid Phase: ITLC-SG

Solvent A: 0.9% Sodium Chloride (for determination of reduced technetium)

Solvent B: Acetone (for determination of pertechnetate)

Step 1

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Add 1 mL of the required solvent to an 18 mm x 150 mm test tube. Stopper and allow the atmosphere in the tube to equilibrate for 1 minute.

Step 2

Place a drop (approximately 0.02 mL) of the radioactive solution on a 1 cm x 10 cm chromatographic strip at a pencil mark 1 cm from one end of the strip, which is the origin. A simple way to do this is to use a standard 1 mL tuberculin syringe with a 25 gauge needle and dispense one small drop. Discard the needle and syringe after use. Instead of a tuberculin syringe a 20 microlitre disposable micropipette (e.g. Fisher Scientific 21-164-2D) can also be used to dispense 0.02 mL.

Immediately dry the spot using a gentle stream of nitrogen gas. Do not use compressed air since this tends to cause pertechnetate formation.

Step 3

Develop the chromatogram by placing it, with the origin down into the solvent, in the previously equilibrated test tube. Stopper the test tube. The test tube should be kept upright, ideally in a test tube rack. Development requires about 10 minutes for ITLC-SG strips.

Step 4

When the solvent front has climbed to the top of the strip, remove it with forceps and allow it to dry. The strips can be dried by placing them radioactive side up on a disposable non-porous pad at room temperature.

In the saline system, reduced $^{99m}TcO_2$ stays at the origin (R_f 0), while the bound and free technetium $^{99m}TcO_4^-$ move to the front R_f 0.85 to 1.0.

In the acetone system, the bound and reduced fractions stay at the origin while free pertechnetate $^{99m}TcO_4^-$ migrates to the front R_f 0.85 to 1.0.

Step 5

Method A - Determination of reduced technetium, using saline solvent:

Cut the dried strip 3 cm from the origin. The short piece is marked as *Part I* and the long piece is marked as *Part II*. Count the pieces in a suitable counter and determine the percentage of reduced technetium according to the following formula:

$$\text{Percent } ^{99m}TcO_2 = \frac{\text{Counts in } Part\ I}{\text{Counts in } Part\ I + Part\ II} \times 100$$

Method B - Determination of pertechnetate using acetone:

Cut the dried strip 2 cm from the solvent front end. The short piece is marked *Part IV* and the long piece is marked *Part III*. Count the pieces in a suitable counter and determine the percentage of free pertechnetate according to the following formula:

$$\text{Percent } ^{99m}TcO_4^- = \frac{\text{Counts in } Part\ IV}{\text{Counts in } Part\ III + Part\ IV} \times 100$$

NOTE: IT IS IMPORTANT TO NOTE THAT THE STRIPS ARE CUT IN DIFFERENT POSITIONS FOR METHODS A AND B.

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Step 6

Determine the amount of bound technetium according to the following formula:

Percent chelated $^{99m}Tc = 100 - \% \, ^{99m}TcO_4^- - \% \, ^{99m}TcO_2$

Step 7

Store all waste radioactive strips for 48 hours before disposing of them as non-radioactive waste. Store used chromatographic solvents in a similar fashion.

4.8 Radiation Dosimetry

The estimate absorbed radiation doses to various organs of an average patient (70 kg) from an intravenous injection of a maximum dose of 740 MBq (20 mCi) of Technetium Tc 99m Medronate injection are shown in Table 1. The effective half-life is assumed to be the physical half-life for all calculated values.

Table 1. Estimated Absorbed Radiation Doses

Organ / Tissue	mGy / 740 MBq	Rads / 20 mCi
Total Body	1.3	0.13
Total Bone	7.0	0.70
Red Marrow	5.6	0.56
Kidneys	8.0	0.80
Liver	0.6	0.06
Bladder Wall		
2.0 hr void	26.0	2.60
4.8 hr void	62.0	6.20
Ovaries		
2.0 hr void	2.4	0.24
4.8 hr void	3.4	0.34
Testes		
2.0 hr void	1.6	0.16
4.8 hr void	2.2	0.22

5 OVERDOSAGE

In the event of the administration of a radiation overdose with Technetium Tc 99m Medronate injection, if the patient's medical condition allows, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body via forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose to the patient.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

MDP (Kit for the preparation of Technetium Tc 99m Medronate injection) is available in cartons

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containing 10 reaction vials, each reaction vial containing, in lyophilized form, sterile and non-pyrogenic:

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous	Solution for Injection 10 mg/vial Medronic Acid (as Na salt)	para-Aminobenzoic Acid - 2 mg, Stannous Chloride Dihydrate - 1.1 mg

The pH is adjusted with HCl and/or NaOH prior to lyophilization. The pH of the reconstituted radiopharmaceutical is 6.5 to 7.5. The vials are sealed under an atmosphere of nitrogen.

Labels with radiation warning symbols and a package insert are supplied in each carton.

6.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies is listed in Table 2.

Table 2. Principal Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

6.2 External Radiation

The specific gamma ray constant for Technetium Tc 99m is 5.44 mcC·Kg^{-1}·MBq^{-1}·hr^{-1} (0.78 R/mCi-hr) at 1 cm. The first half value layer is 0.017 cm of lead. To facilitate control of the radiation exposure from megabecquerel amounts of this radionuclide, the use of a 0.25 cm thickness of lead will attenuate the radiation emitted by a factor of about 1000. A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of lead is shown in Table 3.

Table 3. 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 intervals after the time of calibration are shown in Table 4.

Table 4. Physical Decay Chart of Technetium Tc 99m Half Life: 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining

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0*	1.000	5	0.562
1	0.891	6	0.501
2	0.794	8	0.398
3	0.708	10	0.316
4	0.631	12	0.251

* Calibration Time

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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.

The contents of the reaction vial are intended **ONLY** for use in the preparation of Technetium Tc 99m Medronate injection and are **NOT** to be administered directly to the patient.

The technetium Tc 99m labelling reactions involved in preparing the agent depend on maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc 99m solution may thus adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc 99m solutions containing oxidants should not be employed.

The contents of the kit before preparations are not radioactive. However, after the sodium pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained.

Carcinogenesis and Mutagenesis

No long term animal studies have been performed to evaluate carcinogenic potential of Tc 99m Medronate injection. Mutagenesis studies have not been conducted.

Endocrine and Metabolism

Hypocalcemia

The diphosphonate class of compounds is known to complex cations such as calcium and can create hypocalcemia as observed in animal models (see 16 NON-CLINICAL TOXICOLOGY). Therefore, caution should be exercised when administering this agent to patients who have, or who may be predisposed to hypocalcemia (i.e. alkalosis).

Immune

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Sensitivity

Hypersensitivity reactions, including very rare instances of anaphylaxis, have been reported during diagnostic use of Tc 99m Medronate injection. Obtain a history of allergy or hypersensitivity in all patients prior to use and avoid using if a patient is allergic to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see 2 CONTRAINDICATIONS). Monitor for sensitivity reactions and have access to cardiopulmonary resuscitation equipment and personnel (see 4.1 Dosing Considerations).

Radiation Exposure

Technetium Tc 99m contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Use the lowest dose of Tc 99m Medronate injection necessary for imaging.

Encourage patients to drink fluids and bladder void as frequently as possible after intravenous administration (see 4.1 Dosing Considerations).

Reproductive Health: Female and Male Potential

Studies have not been performed to evaluate whether Technetium Tc 99m Medronate has an effect on fertility in males or females.

Risk for Image Misinterpretation

Urinary bladder activity, faint renal activity, and minimal soft-tissue activity are normally present in healthy individuals. The patient's medical conditions and/or concomitant medications may result in soft tissue uptake (see 9.4 Drug-Drug Interactions).

The finding of an abnormal osseous concentration of radioactivity implies the existence of underlying pathology, but further study is required to distinguish benign from malignant lesions. The quality of the image may be affected by obesity, old age, and impaired renal function.

Other image acquisition studies might impair or be impaired by bone imaging procedure. The impairment may result in false-positive or false negative images. It is recommended, where feasible, that the sequence of image acquisition studies be scheduled to reduce such interference. Alternatively, a different imaging agent for concomitant studies may be employed to avoid or reduce impairment.

7.1 Special Populations

7.1.1 Pregnant Women:

No animal reproductive studies have been conducted with Tc 99m Medronate.

It is not known whether Tc 99m Medronate injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women.

Limited published literature describes Tc 99m Medronate crossing the placental barrier. No adverse fetal effects or radiation-related risks have been identified for diagnostic procedures involving less than 50 mGy, which represents less than 10 mGy fetal doses .

All radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of

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development and the magnitude of the radiation dose.

Tc 99m Medronate injection should only be given to a pregnant woman if clearly needed and only after the patient is informed about the potential for adverse pregnancy outcomes based on the radiation dose from Technetium Tc 99m Medronate and the gestational timing of exposure.

7.1.2 Breast-feeding

Free Tc 99m is excreted in human milk during lactation. Mothers may nurse the infant just before administration of Technetium Tc 99m Medronate Injection. If required, formula feeding could be substituted for breast feeding for at least 6 hours following administration of the product. After expressing the milk completely and discarding it, breast feeding may resume.

The mother's clinical need for Tc 99m Medronate should be considered including any potential adverse effects on the breastfed child from Tc 99m Medronate or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available; therefore, it has not been authorized an indication for pediatric use. The radiation risk of Technetium Tc 99m is greater in pediatric patients than adults.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No formal registrational studies of Technetium Tc 99m Medronate in the elderly were performed to determine whether they respond differently from younger subjects. In general, dose selection for a geriatric patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8 ADVERSE REACTIONS

8.1 Adverse Drug Reaction Overview

The most common adverse reactions reported in patients receiving Technetium Tc 99m Medronate injection are nausea, rash, and other skin irritations such as dermatitis, urticaria and pruritus.

At least one death secondary to cardiac arrest following the administration of Technetium Tc 99m Medronate has been reported, with insufficient information to determine a causal relationship.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified from post-marketing surveillance. Because these reactions are voluntarily reported from a population of uncertain size, it is not always possible to reliably estimate their exact frequency or establish the causal relationship to Technetium Tc 99m Medronate exposure against the patient's pre-existing medical condition.

Adverse reactions are presented per alphabetical system organ class and in decreasing order of frequency:

- Cardiac disorders: arrhythmia, cardiac arrest.
- Gastrointestinal disorders: nausea, vomiting.

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- General disorders and administration site conditions: chills, asthenia, pyrexia, malaise, peripheral swelling, chest discomfort, swelling.
- Hepatobiliary disorders: jaundice.
- Immune system disorders: hypersensitivity.
- Musculoskeletal and connective tissue disorders: myalgia, arthralgia.
- Nervous system disorders: dizziness, headache, syncope.
- Respiratory, thoracic and mediastinal disorders: dyspnoea, cough.
- Skin and subcutaneous tissue disorders: pruritus, rash, urticaria, erythema, dermatitis.
- Vascular disorders: hypotension, flushing.

Reporting of suspected adverse reactions

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://sideeffects.health.gov.il).

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

No interaction studies have been performed.

Potential interactions with the results of the bone scan have been described. A modified accumulation of the radiotracer (in bone and/or soft tissue) is reported in concomitant administration of iron containing compounds, acute administration of diphosphonate, several cytostatic and immunosuppressive drugs, aluminium-containing drugs, contrast media, antibiotics, and anti-inflammatory substances.

As etidronate reduces Technetium Tc 99m Medronate bone scintigraphy sensitivity, through bone metabolism reduction and direct binding site competition, bone scintigraphy should be carried out before or earliest 2 to 4 weeks after etidronate disodium therapy administration.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

When injected intravenously, Technetium Tc 99m Medronate is rapidly cleared from the blood; about 50% of the dose is accumulated and retained by the skeleton, while the remaining 50% is excreted in the urine within 24 hours. About 10% of the injected dose remains in the blood at 1 hour post-injection, 5% at 2 hours, and less than 1% remains at 24 hours. The resultant blood clearance curve

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is tri-exponential with the two fastest components accounting for all but a few percent of the injected dose.

10.2 Pharmacodynamics

Following intravenous administrations of Technetium Tc 99m Medronate, skeletal uptake occurs as a function of blood flow to bone and bone efficiency in extracting the complex. Bone mineral crystals are generally considered to be hydroxyapatite, and the complex appears to have an affinity for the hydroxyapatite crystals in the bone.

10.3 Pharmacokinetics

The rapid blood clearance provides bone to soft-tissue ratios which favour early imaging. The skeletal uptake is bilaterally symmetrical and is greater in the axial skeleton than in the long bones. Areas of abnormal osteogenesis show altered uptake making it possible to visualize a variety of osseous lesions.

11 STORAGE, STABILITY AND DISPOSAL

The unreconstituted reaction vials should be stored at or below room temperature (2 °C to 30 °C). After labelling with technetium Tc 99m, the radiopharmaceutical should be stored at cool temperature 2 °C to 8 °C.

The expiry date of the product is indicated on the packaging materials.

12 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.

Radiopharmaceuticals should be used by or under the control of health professionals who are qualified by specific training and experience in the safe use and handling of radionuclide.

13 PHARMACEUTICAL INFORMATION

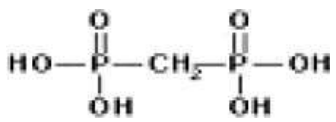
Drug Substance

Proper name: Medronic Acid

Chemical name: Methylene Diphosphonic (MDP) Acid

Molecular formula and molecular mass: $CH_6O_6P_2$ and 176 $g \cdot mol^{-1}$

Structural formula of medronic acid:



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Physicochemical properties: White or almost white powder, amorphous or crystalline, hygroscopic powder. Free from foreign matter.

Product Characteristics

The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Medronate injection for diagnostic use by intravenous injection.

Each 10 mL reaction vial contains 10 mg of medronic acid (as the sodium salt), 1.1 mg of stannous chloride dihydrate, and 2 mg of para-aminobenzoic acid in lyophilized form under an atmosphere of nitrogen.

Sodium hydroxide and/or hydrochloric acid have been used for pH adjustment. The addition of sterile, non-pyrogenic, and oxidant-free sodium pertechnetate Tc 99m solution produces a rapid labelling which is essentially quantitative and which remains stable *in vitro* throughout the 12 hours life of the preparation.

The pH of the reconstituted radiopharmaceutical is 6.5 to 7.5. No bacteriostatic preservative is present.

14. CLINICAL TRIALS

The clinical trial data, on which the original indications were authorized, are not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

A safety assessment using stannous medronate complex reconstituted with saline but without technetium Tc 99m or para-aminobenzoic acid has been made in two rodent and one non- rodent species.

In mice, an intravenous injection of 100 mg/kg (2 mg / 0.2 mL / 20 g) induced severe clonic convulsions. No mortalities and no gross pathological changes were discovered over a 14 day observation period. A lower dose of 40 mg/kg showed no signs of intoxication and the gross necropsy was negative. Similar results were obtained in rats and beagle dogs at 20 mg/kg.

The human dose using this formulation is variable depending on the number of examinations made from the contents of one vial. In the event that this becomes a single dose of 10 mg per 70 kg or 0.15 mg/kg, these results indicated a safety factor of at least 100.

The toxicity of medronic acid has been reported to be the same as that for the ethylene- hydroxy-diphosphonate (EHDP) (intravenous LD_{50} 45 to 55 mg/kg) in mice and rabbits. Other reports showed a maximum (LD_{100}) lethal dose of EHDP in mice to be 200 mg/kg with no deaths occurring at 100 mg/kg. The LD_{50} in rabbits and rats was 40 to 70 mg/kg on rapid injection of EHDP, whereas slow

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injection raised this to 70 to 100 mg/kg. It was demonstrated in a variety of experimental animals that acute toxic symptoms of tachycardia, hyperpnea, and tetany began at 20 to 30 mg/kg. These changes were considered consistent with the induction of hypocalcemia.

The role played by tin chelation, dilution, and speed of injection as factors in explaining the variable results of toxicity studies has been discussed in the literature.

A 14 day subacute toxicity study of stannous medronate complex was performed in mice and cats. In cats, pyelonephritis was observed in the test groups as well as in some of the control animals. Associated renal tubular calcification was noted only in the dosed cats. Minimal focal calcification was observed in the liver and heart of one mouse in the high dose group. No other significant toxicological findings were noted. The cumulative low doses in cats and in mice were 65 and 87 times greater, respectively, than the maximum probable human dose on a mg/kg basis, while the cumulative high doses were 490 and 866 times greater, respectively.

17 MANUFACTURER

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18 REGISTRATION HOLDER

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19 MARKETING AUTHORISATION NUMBER

134-64-29992-00

Revised in June 2022 according to MOH guidelines