PRESCRIBING INFORMATION

AMERSCAN® MEDRONATE II

(Agent for use in the preparation of Technetium Tc-99m
Medronate Injection for bone scintigraphy)

Radiodiagnostic Agent

GE Healthcare Canada Inc.
2300 Meadowvale Blvd.,
Mississauga, Ontario
L5N 5P9

Date of Approval: January 19, 2011

Control #:142144

AMERSCAN® MEDRONATE II

Agent for use in the preparation of Technetium Tc-99m Medronate Injection for bone scintigraphy.

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Radiodiagnostic Agent

DESCRIPTION

The kit contains five multidose vials for preparing technetium-99m labelled medronate for bone scintigraphy. Each 10 ml vial contains a sterile pyrogen-free freeze-dried mixture of 5 mg medronic acid (as sodium salt), 0.34 mg stannous fluoride and 2 mg sodium p-aminobenzoate*, sealed under an inert nitrogen atmosphere with a rubber closure. Upon reconstitution with eluate from a technetium –99m generator, a stabilized, sterile pyrogen-free solution is produced for intravenous injection. Reconstitution is a one- step procedure where the addition of technetium-99m pertechnetate to the freeze-dried contents of the vial causes reduction of the pertechnetate and formation of a soluble technetium-99m/medronic acid complex. The pH of the preparation lies in the range pH5.5 – pH7.5.

Physical Characteristics of Tc-99m

Technetium Tc-99m decays by isometric transition with a physical half-life of 6.02 hours.[1] Photons that are useful for detection and imaging studies are listed in Table 1.

---

[1] Martin, M.J. ed., Nuclear Decay Data for Selected Radionuclides, p.24, ORNL 5114, March 1976.

*Canadian Patent 1, 190,473

Table 1. Principal Radiation Emission Data

Radiation	Mean % Disintegration	Mean Energy (KeV)
Gamma-2	88.96	140.5

External Radiation

The specific gamma ray constant for Tc-99m is 206 μC kg^{-1}/37MBq-hr. (0.8R/millicurie-hr.) at 1cm. The first half-value layer is 0.2mm of Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. For example, the use of a 2.5mm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0.2	0.5
0.8	10^{-1}
1.6	10^{-2}
2.5	10^{-3}
3.3	10^{-4}

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

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

Hours	Fraction Remaining	Hours	Fraction Remaining
-5	1.778	5	0.562
-4	1.585	6	0.501
-3	1.413	7	0.447
-2	1.259	8	0.398
-1	1.122	9	0.355
0*	1.000	10	0.316
1	0.891	11	0.282
2	0.794	12	0.251
3	0.708	18	0.126
4	0.631	24	0.063

*Calibration time

CLINICAL PHARMACOLOGY

The affinity of certain phosphate compounds for bone has been well documented ([14,17]). The labelling of such a compound with technetium-99m, a nuclide with radiation characteristics almost ideal for scintigraphy, produced the first technetium-99m bone scanning agent ([18]). Since that time, a number of phosphate compounds have been labelled with technetium-99m in search of a stable, efficacious product ([19]). The introduction of technetium-99m labelled medronic acid (MDP) ([1]) has provided an agent for bone scintigraphy which satisfies these criteria better than any previous agent ([3]).

INDICATIONS AND USAGE

The injection prepared according to the outline of the procedure is indicated for skeletal scintigraphy especially for the detection of pathological osteogenesis ([1,3]). Scintigraphy has proved valuable in the detection of bone metastases secondary to bronchogenic carcinoma ([4]), breast carcinoma ([5,6]) and prostate carcinoma ([7]). Additionally it has been found useful in the detection and delineation of lesions of osteogenic sarcoma ([8]), osteomyelitis ([9,10]) and Paget's disease ([11,13]).

CONTRAINDICATIONS

No specific contraindications are known. Hypersensitivity to the active substance or to any of the excipients.

WARNINGS

The possibility of hypersensitivity, anaphylactic and anaphylactoid reactions, including life-threatening anaphylaxis should always be considered.

Patients should be observed for at least 30 minutes. Health Care Providers should be prepared to manage life-threatening anaphylaxis and advanced life support facilities should be readily available.

The possibility of hypersensitivity including serious anaphylactic/anaphylactoid reactions should always be considered.

Radiopharmaceuticals should be used only by or under the control of 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 authorized to license the use of radionuclides.

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.

Where an assessment of the risk/benefits ratio suggests use of this product in lactating mothers, nursing should be stopped.

Adequate studies do not exist to support the use in children. As in pregnancy and lactating mothers, the benefit to risk ratio should be assessed before consideration is given to the use of this product in this age group.

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.

PRECAUTIONS

The contents of the Medronate II kit are intended for use in the preparation of Technetium Tc-99m labelled medronate and are NOT to be directly administered to the patient.

The contents of the kit are not radioactive. However, after the sodium pertechnetate Tc-99m is added, adequate shielding of the final preparation must be maintained. As in the use of any other radioactive material, care should be taken to insure minimal radiation exposure to the patient, consistent with proper patient management and to insure minimum radiation exposure to occupational workers.

To minimize radiation dose to the bladder, the patients should be encouraged to drink fluids and to void immediately before the examination and as often thereafter as possible for the next 4-6 hours.

ADVERSE REACTIONS

Occasionally (approximately 0.5 out of 100,000 investigations) hypersensitivity reactions, including very rare life-threatening anaphylaxis, may occur following intravenous administration of technetium [99m Tc] medronate.

A local rash or more usually a generalized rash with itching have been reported; onset of the reaction is usually several hours after the injection and it may last up to 48 hours. Sweating without any rash has been reported as well. Treatment is symptomatical.

Other reactions reported include a fall in blood pressure and hypotensive symptoms, nausea, vomiting, cutaneous vasodilation, headache, malaise, oedema of the extremeties and arthralgia.

DOSAGE AND ADMINISTRATION

The suggested adult dose to be employed in the average patient (70 kg) is 370-555 MBq (10-15 mCi) by intravenous injection. Imaging should commence at least two hours after injection.

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

RADIATION DOSIMETRY

The absorbed radiation doses per injected 40MBq (1mCi) technetium-99m labelled medronate bone agent are estimated to be:

Skeleton	0.6mGy	(0.06rad)
Bone Marrow	0.4mGy	(0.04rad)
Kidneys	0.1mGy	(0.01rad)
Bladder Wall	2.5mGy	(0.25rad)
Testes	0.1mGy	(0.01rad)
Ovaries	0.2mGy	(0.02rad)
Whole Body	0.2mGy	(0.02rad)

ADDITIONAL ACCESSORIES REQUIRED

Lead shield

10ml syringe and needle (see note 3)

Saline for injection (see note 2)

Tongs or forceps

PROCEDURE

Use aseptic technique throughout.

1. Place one of the vials in a suitable shielding container and swab the rubber closure with the sterilizing swab provided.
2. Using a 10 ml syringe, inject between 2 and 8 mls of eluate from a technetium-99m sterile generator into the shielded vial (see notes 1 and 2). Before removing the syringe from the vial, withdraw an equal volume of gas from the space above the solution to normalize the pressure in the vial.

3. Shake the shielded vial for 10 seconds to ensure complete dissolution of the powder.
4. Assay the total activity, complete the label provided and attach to vial.
5. Incubate the injection for 15 minutes at room temperature.
6. The preparation may be stored at any temperature in the range of 2-25^{o}C but should be administered within 8 hours after reconstitution.

NOTES

1. Up to 18.5GBq (500mCi) technetium-99m may be added to the vial. The sodium pertechnetate technetium-99m solution should be oxidant-free.
2. If the radioactive concentration of technetium-99m in the generator eluate is higher than needed for the patient doses, a small volume of eluate containing sufficient technetium-99m activity should be diluted with additive-free saline for injection to final volume between 2 and 8 ml before being used in step 2.
3. Certain syringes have been found to contain water soluble components which can complex with reduced technetium-99m. This can impair scan quality. The effect can be eliminated by use of an all-plastic syringe for handling eluate and saline prior to reconstitution of the agent.
4. Before use, the prepared radiopharmaceutical should be visually inspected and not be used if there is evidence of foreign matter.

QUALITY CONTROL

It is recommended that the radiochemical purity of the prepared radiopharmaceutical be checked prior to administration.

Radiochemical Purity Measurement

A combination of two chromatographic systems is necessary for the determination of the radiochemical purity of the injection.

Test samples are applied by needle approximately 2.5cm from the bottom of a Varian SA chromatography paper strip (2 cm x 20 cm) and a Whatman 3MM chromatography paper strip (2cm x 30cm). The strips are then immediately placed in prepared ascending chromatography development tanks, one containing acetone and the other containing 0.1M citric acid solution (1cm depth fresh solvent). After a 15cm elution the strips are removed, solvent fronts marked, the strips dried and the distribution of activity determined using suitable equipment.

Interpretation of chromatograms

System 1 (Whatman 3MM:acetone)

Technetium-99m medronate complex and colloidal technetium remain at the origin. Pertechnetate migrates at Rf 0.8-1.0.

System 2 (Varian SA:0.1M citric acid solution)

Colloidal technetium remains at the origin.Technetium-99m medronate complex and pertechnetate migrate at Rf 0.8-1.0.

The percentage of radioactivity corresponding to pertechnetate ion is obtained from system 1. This should be not greater than 2.0%.

The sum of the percentages of impurities obtained from systems 1 (pertechnetate) and system 2 (Hydrolysed technetium and colloidal technetium) should be not greater than 5%.

HOW SUPPLIED

The kit contains five multidose vials for preparing technetium-99m labelled medronate for bone scintigraphy. Each vial contains a pre-dispensed freeze-dried, sterile pyrogen-free formulation intended for reconstitution with eluate from a technetium-99m generator. This produces a stabilized solution containing a bone seeking technetium complex for intravenous injection.

CONTENTS (5 of each)

10ml vial containing a freeze-dried mixture of sodium medronate, stannous fluoride and stabilizer.

Labels for reconstituted injection

Swabs (70% isopropyl alcohol BP)

Pack Leaflet

STORAGE

Store at any temperature in the range of 2-25^{o}C. Store the reconstituted injection at 2-25^{o}C.

REFERENCES

1. SUBRAMANIAN, G., BLAIR, R.J., KALLFELZ, F.A., THOMAS, F.D. and McAFEE, J.G. Tc-99m MDP (methylene diphosphonate): a superior agent for skeletal imaging (Abstract only). Journal of Nuclear Medicine, vol. 14, p. 640, 1973.

2. SUBRAMNIAN, G., McAFEE, J.G., BLAIR, R.J., KALLFELZ, F.A. and THOMAS, F.D. Technetium-99m methylene diphosphonate a superior agent for skeletal imaging: comparison with other technetium complexes. Journal of Nuclear Medicine, vol. 16 pp. 774-755, 1975.

3. DAVIS, M.A. and JONES, A.G. Comparison of Tc-99m-labelled phosphonate and phosphate agents for skeletal imaging. Seminars in Nuclear Medicine, vol. 6, pp. 19-31, 1976.

4. SHIRAZI, P.H., STERN, A.J., SIDELL, M.S., RAYUDU, G.V.S. and FORDHAM, E.W. Bone scanning in the staging and management of bronchogenic carcinoma: review of 206 cases. (abstract only), Journal of Nuclear Medicine, vol. 14, p.451, 1973.

5. FRANKEL, R.S., RICHMAN, S.D., LEVENSON, S.M., NELSON, R.L., INGLE, J.N., TORMEY, D.C., JONES, A.E. and JOHNSTON, G.S.
Bone scintigraphy in breast carcinoma (abstract only), Journal of Nuclear Medicine, vol. 15, p.491, 1974

6. FRIEDMAN, B.H., SIEGEL, M.E. and WAGNER, H.N. Breast uptake of Tc-99m HEDSPA (diphosphonate): an indicator of breast carcinoma. (Abstract only), Journal of Nuclear Medicine, vol. 15, pp. 491-492, 1974.

7. MIKI, M., MACHIDA, I. and MINAMI, T. Evaluation of technetium-labelled pyrophosphate scintigraphy for detection of bone metastases from prostatic carcinoma. (Abstract only), Journal of Nuclear Medicine, vol. 15, p517, 1974.

8. BROWER, A.C. and TEATES, C.D. Positive TC-99m polyphosphate scan in case of metastatic osteogenic sarcoma and hypertrophic pulmonary osteoarthropathy. Journal of Nuclear Medicine, vol. 15, pp. 53-55, 1974.

9. WAXMAN, A.D., BRYAN, D. and SIEMSEN, J.K. Bone scanning in the drug abuse patient:early detection of hematogenous osteomyelitis. Journal of Nuclear Medicine, vol. 14, pp. 647-650, 1973.

10. SIEMSEN, J.K. and WAXMAN, A.D. Early diagnosis of hematogenous osteomyelitis. (Abstract only), Journal of Nuclear Medicine, vol. 15, pp. 533, 1974.

11. SHIRAZI, P.H., RYAN, W.G. and FORDHAM, E.W. Bone scanning in evaluation of Paget's disease of bone. CRC Critical Reviews in Clinical Radiology and Nuclear Medicine, vol. 5, pp. 523-558, 1974.

12. MILLER, S.W., CASTRONOVO, H.P., PENDERGRASS, H.P. and POTSAID, M.S.Technetium-99m labelled diphosphonate bone scanning in Paget's disease. American Journal of Roentgenology, vol. 121, pp. 177-183, 1974.

13. SERAFINI, A.N. Paget's disease of bone. Seminars in Nuclear Medicine, vol. 6, pp. 47-58, 1976.

14. HAROLD, F.M. Inorganic polyphosphates in biology: structure, metabolism and function, Bacteriological Reviews, vol. 30, pp. 772-794, 1966.

15. FELS , I.G., KAPLAN, E., GRECO, J. and VEATCH, R.Incorporation in vivo of phosphorus-32 from condensed phosphates. Proceedings of the Society for Experimental Biology and Medicine, vol. 100, pp. 53-55, 1958.

16. KAPLAN, E., FELS, I.G., KOTLOWSKI, B.R., GRECO, J. and WALSH, W.S. Therapy of carcinoma of the prostate metastatic to bone with ^{32}P-labelled condensed phosphate. Journal of Nuclear Medicine, vol. 1, pp. 1-13, 1960.

17. BIGLER, R.E., ROSEN, G., TOFE, A.J., RUSS, G.A., FRANCIS, M.D., BENUA, R.S., WOODWARD, H.Q. and KOSTICK, J.A. Comparative distribution of ^{32}P and Tc-99m diphosphonates in patients with osteogenic sarcoma. (Abstract only), Journal of Nuclear Medicine, vol 17, p. 548, 1976.

18. SUBRAMANIAN, G. and McAFEE, J.G. A new complex of Tc-99m for skeletal imaging. Radiology, vol.99, pp. 192-196, 1971.

19. MERRICK, M.V. Review article-bone scanning, British Journal of Radiology, vol. 48, pp. 327-351, 1975.