

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amerscan Medronate II Agent 6.25 milligrams kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylene diphosphonic acid 6.25 milligrams/vial (as the sodium salt), equivalent to 5.0mg medronic acid/vial.

Amerscan Medronate II Agent is reconstituted with Sodium Pertechnetate (^{99m}Tc) Injection (not included in this kit) to prepare Technetium (^{99m}Tc) Medronate Injection.

Technetium-99m disintegrates 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 product before reconstitution contains:

- Sodium: 1.60 mg/vial. This needs to be taken into consideration for patients on a controlled sodium diet.
- Sodium p-aminobenzoate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation
White to off-white powdery solid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

After reconstitution with Sodium Pertechnetate (^{99m}Tc) Injection the agent may be used for bone scintigraphy, where it delineates areas of altered osteogenesis.

4.2 Posology and method of administration

The average activity administered by a single intravenous injection is 500MBq (300-700MBq). Other activities may be justifiable.

Images obtained shortly after injection (e.g. in the so-called "3-phase bone scan" procedure) will only partly reflect metabolic bone activity. Late phase static scintigraphy should be performed not earlier than 2 hours after injection.

The patient should void before scanning.

The dose to be administered to a child should be a fraction of the adult dose calculated from the body weight according to the following table.

Table: **Dose calculation for use of Technetium (^{99m}Tc) Medronate Injection in Children**

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 Medicines)

In very young children (up to 1 year) a minimum dose of 40MBq is necessary in order to obtain images of sufficient quality.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

The possibility of hypersensitivity including serious anaphylactic/ anaphylactoid reactions should always be considered. Advance life support facilities should be readily available.

This product contains sodium p-aminobenzoate. This may increase the risk of jaundice in newborn babies.

In infants and children particular attention should be paid to the relatively higher radiation exposure of the epiphyses in growing bone.

Appropriate precautions should be taken concerning the activity, which is eliminated by the patients, to avoid any contamination. To reduce the radiation exposure to the bladder wall, sufficient hydration of the patient and frequent voiding is recommended.

To avoid accumulation of tracer in the musculature it is advised that strenuous exercise be discouraged immediately after injection until satisfactory bone imaging has been effected.

Inadvertent or accidental subcutaneous administration of technetium-99m medronate should be avoided as perivascular inflammation has been described for technetium-99m diphosphonates.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions have been described. An increased extraosseous accumulation of the radiotracer is reported for 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

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 700MBq technetium-99m medronate to a patient with normal bone uptake results in an absorbed dose to the uterus of 4.27mGy. The dose decreases to 2.03mGy in patients with high bone uptake and/or severely impaired kidney function. Doses above 0.5mGy would be regarded as a potential risk for 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, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, one breast-feed should be banked prior to injection and the subsequent one discarded after injection. Breast feeding can be restarted 4 hours post injection.

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

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 medronate. Cases of local rash or generalized 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 H₁ antagonist is helpful.

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

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 effective dose is less than 20mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

In the event of the administration of a radiation overdose with technetium-99m medronate, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and bladder voiding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, technetium (^{99m}Tc) compounds, technetium (^{99m}Tc) medronic acid, ATC code: V09B A02

At the chemical concentrations of radiopharmaceutical and excipients used for diagnostic procedures technetium -99m medronate does not appear to exert any pharmacodynamic effect.

5.2 Pharmacokinetic properties

In the first 3 minutes after injection of technetium-99m medronate there is soft tissue uptake and renal accumulation. With increasing clearance from these compartments, progressive accumulation in the skeletal system is seen initially in the lumbar vertebrae and the pelvic region. Blood clearance proceeds in 3 phases: 1: rapid phase (t_{1/2} = 3.5 min.), 2:

medium phase ($t_{1/2} = 27$ min.) and 3: slow phase ($t_{1/2} = 144$ min.). The rapid phase represents the transfer of the radioactive substance from the circulation into the extravascular system, the medium phase involving skeletal uptake. The slow phase is probably associated with the release of the technetium-99m medronate complex from a protein bound complex. About 50% of the dose injected accumulates in the skeleton. Maximum bone accumulation is reached 1 hour after injection and remains practically constant up to 72 hours. The circulating unbound complex is eliminated via the kidneys.

The peak of activity through the kidneys is reached after approximately 20 minutes. Within 1 hour, with normal renal function, around 32% of the total quantity of unbound complex has undergone glomerular filtration, within 2 hours 47.5% and within 6 hours 60%. The quantity of phosphonate, within the recommended dose range, has no effect on renal excretion. The quantity eliminated via the intestines is insignificant.

The level of accumulation in the skeletal system depends on the circulation and the extent of regeneration of basic bone material. Whole body retentions of $31.6 \pm 5\%$ are reported in healthy individuals, $38.2 \pm 7\%$ in those with extensive metastases, $49 \pm 11\%$ in primary hyperparathyroidism and 45% in osteoporosis.

5.3 Preclinical safety data

This agent is not intended for regular or continuous administration. Mutagenicity studies and long-term carcinogenicity studies have not been carried out. Repeated dose toxicity studies in rats with 50-100 times the human dose does not cause macroscopic or microscopic alterations. Repeated administration of very high doses of diphosphonates can cause mineralization disorders.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous fluoride
Sodium p-aminobenzoate

6.2 Incompatibilities

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

6.3 Shelf Life

78 weeks from the day of manufacture.

The reconstituted product should be stored below 25°C. Do not freeze. The reconstituted product should be injected within 8 hours of reconstitution.

6.4 Special precautions for storage

Store below 25°C.

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

6.5 Nature and contents of container

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

Pack size: kit containing 5 multidose vials.

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

GE Healthcare Limited,
Amersham Place,
Little Chalfont,
Buckinghamshire
HP7 9NA
United Kingdom.

8 MARKETING AUTHORISATION NUMBER

PA 240/22/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th February 1999

Date of last renewal: 5th February 2009

10 DATE OF REVISION OF THE TEXT

July 2010

11 DOSIMETRY

The table below shows the dosimetry as calculated according to the Publication 80 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1998.

Radiation exposure (normal bone uptake) as absorbed dose/injected activity (mGy/MBq).

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15years	10 years	5 years	1 year
Adrenals	2.1E-03	2.7E-03	3.9E-03	5.8E-03	1.1E-02
Bladder	4.8E-02	6.0E-02	8.8E-02	7.3E-02	1.3E-01
Bone surfaces	6.3E-02	8.2E-02	1.3E-01	2.2E-01	5.3E-01
Brain	1.7E-03	2.1E-03	2.8E-03	4.3E-03	6.1E-03
Breast	7.1E-04	8.9E-04	1.4E-03	2.2E-03	4.2E-03
Gall bladder	1.4E-03	1.9E-03	3.5E-03	4.2E-03	6.7E-03
GI-tract					
Stomach	1.2E-03	1.5E-03	2.5E-03	3.5E-03	6.6E-03
SI	2.3E-03	2.9E-03	4.4E-03	5.3E-03	9.5E-03
Colon	2.7E-03	3.4E-03	5.3E-03	6.1E-03	1.1E-02

(ULI	1.9E-03	2.4E-03	3.9E-03	5.1E-03	8.9E-03)
(LLI	3.8E-03	4.7E-03	7.2E-03	7.5E-03	1.3E-02)
Heart	1.2E-03	1.6E-03	2.3E-03	3.4E-03	6.0E-03
Kidneys	7.3E-03	8.8E-03	1.2E-02	1.8E-02	3.2E-02
Liver	1.2E-03	1.6E-03	2.5E-03	3.6E-03	6.6E-03
Lungs	1.3E-03	1.6E-03	2.4E-03	3.6E-03	6.8E-03
Muscles	1.9E-03	2.3E-03	3.4E-03	4.4E-03	7.9E-03
Oesophagus	1.0E-03	1.3E-03	1.9E-03	3.0E-03	5.3E-03
Ovaries	3.6E-03	4.6E-03	6.6E-03	7.0E-03	1.2E-02
Pancreas	1.6E-03	2.0E-03	3.1E-03	4.5E-03	8.2E-03
Red marrow	9.2E-03	1.0E-02	1.7E-02	3.3E-02	6.7E-02
Skin	1.0E-03	1.3E-03	2.0E-03	2.9E-03	5.5E-03
Spleen	1.4E-03	1.8E-03	2.8E-03	4.5E-03	7.9E-03
Testes	2.4E-03	3.3E-03	5.5E-03	5.8E-03	1.1E-02
Thymus	1.0E-03	1.3E-03	1.9E-03	3.0E-03	5.3E-03
Thyroid	1.3E-03	1.6E-03	2.3E-03	3.5E-03	5.6E-03
Uterus	6.3E-03	7.6E-03	1.2E-02	1.1E-02	1.8E-02
Remaining organs	1.9E-03	2.3E-03	3.4E-03	4.5E-03	7.9E-02
Effective dose (mSv/MBq)	5.7E-03	7.0E-03	1.1E-02	1.4E-02	2.7E-02

The table below shows the dosimetry as calculated according to the Publication 53 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1987.

Radiation exposure (high bone uptake and/or severely impaired kidney function) as absorbed dose/injected activity (mGy/MBq).

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 year	10 year	5 year	1 year
Adrenals	3.5E-03	5.0E-03	7.2E-03	1.1E-02	2.1E-02
Bladder wall	2.5E-03	3.5E-03	5.4E-03	7.4E-03	1.5E-02
Bone surfaces	1.2E-01	1.6E-01	2.6E-01	4.3E-01	1.0E+00
Breast	2.1E-03	2.1E-03	3.2E-03	5.1E-03	9.6E-03
GI-tract					
Stomach wall	2.6E-03	3.2E-03	5.1E-03	7.3E-03	1.4E-02
Small intestine	3.1E-03	3.8E-03	5.7E-03	8.5E-03	1.6E-02
Upper large intestine	2.9E-03	3.6E-03	5.3E-03	8.6E-03	1.5E-02
Lower large intestine	3.4E-03	4.2E-03	6.5E-03	9.6E-03	1.8E-02
Kidneys	3.0E-03	3.7E-03	5.6E-03	8.7E-03	1.6E-02
Liver	2.7E-03	3.3E-03	4.9E-03	7.5E-03	1.4E-02
Lungs	3.0E-03	3.7E-03	5.3E-03	8.1E-03	1.5E-02
Ovaries	2.9E-03	4.1E-03	5.9E-03	8.9E-03	1.6E-02
Pancreas	3.2E-03	4.0E-03	5.9E-03	8.9E-03	1.6E-02
Red Marrow	1.8E-02	2.3E-02	3.7E-03	7.2E-02	1.4E-01
Spleen	2.6E-03	3.4E-03	5.1E-03	7.8E-03	1.5E-02

Testes	2.3E-03	2.7E-03	3.9E-03	6.0E-03	1.1E-02
Thyroid	2.4E-03	3.7E-03	5.4E-03	8.3E-03	1.4E-02
Uterus	2.9E-03	3.7E-03	5.4E-03	8.2E-03	1.5E-02
Other tissue	3.0E-03	3.6E-03	5.3E-03	8.1E-03	1.5E-02
Effective dose equivalent (mSv/MBq)	8.2E-03	1.1E-02	1.7E-02	2.8E-02	6.1E-02

For this product the effective dose resulting from an administered activity of 700MBq is typically 4.0 mSv (per 70kg individual), (ICRP 80, 1998).

For an administered activity of 700MBq the typical radiation dose to the target organ (bone) is 44.1mGy and the typical radiation dose to the critical organ (bladder wall) is 35mGy.

In cases of high bone uptake and/or severely impaired kidney function, the effective dose equivalent resulting from an administered activity of 700MBq of technetium -99m medronate is 5.7mSv. The typical radiation dose to the target organ is 84mGy and the typical radiation dose to the critical organ (red marrow) is 12.6mGy.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

This radiopharmaceutical may be received, used and administered only by authorized persons in hospitals. Its receipt, storage, use, transfer and disposal are subject to the regulations and the appropriate licenses of the local competent official organizations (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) Place one of the vials in a suitable shielding container and swab the rubber closure with the sanitizing swab supplied.
- (2) Using a 10ml syringe, inject a suitable quantity (see notes 1 and 2) of the eluate from a technetium-99m sterile generator into the shielded vial. Before removing the syringe from the vial, withdraw an equivalent volume of gas from the space above the solution to normalise 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.

Notes:

- (1) Up to 18.5 GBq technetium-99m may be added to the vial.
- (2) Reconstitute with 2-8 ml. The eluate may, if necessary, be diluted to 2-8 ml using saline for injection.
- (3) Images from bone agents based on sodium medronate improve if the prepared injection is stored at room temperature for a short time following reconstitution. It is therefore recommended that 15 minutes or more should normally elapse before injection.
- (4) The use of a technetium-99m pertechnetate solution complying with the specifications prescribed by the USP and BP/Ph.Eur on Sodium Pertechnetate (^{99m}Tc) Injection will yield a preparation of an appropriate quality.

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 two Gelman ITLC/SG strips (2.5 cm x 20 cm). The strips are then immediately placed in prepared ascending chromatography development tanks, one containing butan-2-one and the other 1.0 M sodium acetate (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 (ITLC: butan-2-one methyl ethyl ketone)

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

System 2 (ITLC: 1.0M sodium acetate)

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%.