Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Medronate DRAXIMAGE 10mg Kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg of medronic acid.

The radioisotope is not part of the kit.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation

To be reconstituted with sodium pertechnetate (^{99m}Tc) solution for injection (not included in this kit).

White freeze-dried plug that may break into powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

After reconstitution with sodium pertechnetate (^{99m}Tc) solution, the agent is used for bone scintigraphy for the detection of areas of altered osteogenesis associated with:

Neoplasms:

The detection, staging, and evaluation of response to therapy of primary bone tumors (e.g. Ewing's sarcoma, osteosarcoma)
The detection and follow-up of bone metastases

Non-neoplastic lesions:

As an aid in the evaluation of:

- Osteomyelitis
- Avascular necrosis
- Paget's disease
- Stress fractures, shin splints
- Loose or infected joint prosthesis
- Reflex sympathetic syndrome
- Bone graft viability

Since areas or altered osteogenesis can be detected with high sensitivity but low specificity, additional examinations may be necessary.

4.2 Posology and method of administration

Posology

Adults: The optimal activity of technetium (^{99m}Tc) medronate injection has not been systematically investigated. Injected activity may vary according to patient characteristics, imaging procedures, and imaging equipment.

The average activity administered by a single intravenous injection is 500 MBq (300-740 MBq) as recommended by the EANM, 2003. Other activities may be justifiable. For markedly obese adult patient, activity as high as 11 – 13 MBq / kg may be needed as recommended by SNM, 2003.

Newborns, infants, children and adolescents: The optimal pediatric activity has not been systematically investigated. The activity to be administered to a child should be a fraction of the adult activity calculated from the body weight according to the following table:

EANM Paediatric Task Group Pediatric Activity Schedule

Weight	*% adult activity*	*Weight*	*% adult activity*	*Weight*	*% adult activity*
3 Kg	10%	22 Kg	50%	42 Kg	78%
4 Kg	14%	24 Kg	53%	44 Kg	80%
6 Kg	19%	26 Kg	56%	46 Kg	82%
8 Kg	23%	28 Kg	58%	48 Kg	85%
10 Kg	27%	30 Kg	62%	50 Kg	88%
12 Kg	32%	32 Kg	65%	52-54 Kg	90%
14 Kg	36%	34 Kg	68%	56-58 Kg	92%
16 Kg	40%	36 Kg	71%	60-62 Kg	96%
18 Kg	44%	38 Kg	73%	64-66 Kg	98%
20 Kg	46%	40 Kg	76%	68 Kg	99%

In children, a minimum activity of 20 - 40 MBq is necessary in order to obtain images of sufficient quality.

Patients aged 65 and older: The need for dosage adjustments in geriatric populations has not been systematically investigated. Decreased renal function (see below) and decreased osteogenesis in the elderly may affect the uptake, distribution, or elimination of technetium (^{99m}Tc) medronate injection.

Patients with renal impairment: The need for dosage adjustments as a result of renal failure has not been systematically investigated.

Patients with hepatic impairment: The need for dosage adjustments as a result of liver failure has not been systematically investigated. Since technetium (^{99m}Tc) medronate is almost exclusively eliminated by the kidneys, liver failure would not be expected to require an adjustment to the activity administered.

Method of administration of and scintigraphy examination:

For patient preparation see section 4.4.

This medicinal product must be reconstituted before use. When reconstituted with sodium pertechnetate (^{99m}Tc) solution, the clear isotonic solution has a pH of 6.5 to 7.5.

This product is only for intravenous injection.

This medicinal product must be exclusively administered by authorised personnel (see "General warnings" in section 4.4).

Because of potential tissue damage, extravasal injection of this radioactive product has to be strictly avoided.

Image acquisition parameters and procedures will vary depending upon the clinical question and the type of equipment available. The optimal time from dosing to imaging has not been systematically investigated. Images may be obtained early after injection (in the so-called 3-phase bone scintigraphy procedure) to search for abnormal blood flow supply to a part of the skeleton, and some minutes later to evidence a potential rapid uptake by some part of the skeleton. Images are generally acquired 2 to 5 hours after the administration of technetium (^{99m}Tc) medronate injection. Later images (6-24 h) result in a higher target-to-background ratio and may permit better evaluation of the pelvis if this was obscured by bladder activity on the routine (2-5 h) images. Six- to 24-hr delayed imaging may be particularly helpful in patients with renal insufficiency or peripheral circulatory disorders and those with urinary retention.

For detailed instructions on the correct administration/use of this product, see section 12.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Indication of the examination

For all patients: the radiation exposure must be justifiable by the expected diagnostic information achieved with the lowest possible radiation dose.

In pediatric population (aged less than 18): it should be taken into consideration that the effective dose per MBq is higher in children than in adults (see section 11 "Dosimetry"). Particular attention should be paid to the relatively higher radiation exposure of the epiphyses in growing bone

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the study in order to reduce radiation.

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

General warnings

Inadvertent or accidental subcutaneous administration of technetium (^{99m}Tc) medronate should be avoided as perivascular inflammation has been described for technetium (^{99m}Tc) diphosphonates.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations. Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions, should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

The possibility of the occurrence of hypersensitivity reactions including serious anaphylactic / anaphylactoid reactions should always be considered. If a hypersensitivity reaction occurs the administration of the medicinal product must be interrupted immediately and -if necessary- an intravenous treatment initiated. As in case of emergency immediate action is required, advanced life support facilities including the respective medicinal products necessary for treatment should be readily available.

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 medicinal products, aluminium-containing antacids, X-ray contrast media, antibiotics, anti-inflammatory substances, injections of calcium gluconate or heparin calcium and γ-amino caproic acid.

As Etidronate inhibits bone absorption of medronate, bone scintigraphy should be carried out before or earliest 2 – 4 weeks after etidronate administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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, alternative techniques which do not involve ionising radiation should be considered.

Pregnant women

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only imperative investigations should be carried out during pregnancy when likely benefit exceeds the risk incurred by mother and foetus.

Based on published models, administration of 500 MBq technetium (^{99m}Tc) medronate injection to a patient with normal bone uptake results in an absorbed dose to the uterus of 3.15 mGy. The dose decreases to 1.45 mGy in patients with high bone uptake and/or severely impaired kidney function. Published reports in pregnant patients have estimated radiation doses to the fetus to have been 2.6 to 4.6 μGy/MBq (1.3 to 2.3 mGy / 500 MBq). Although this level of radiation is unlikely to present increased risk to the foetus, use of Medronate DRAXIMAGE during pregnancy is not recommended unless clearly necessary.

Breast-feeding mothers

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, breast-feeding should be interrupted for 12 hours and the expressed feeds discarded.

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 all patients: the radiation exposure must be justifiable by the expected diagnostic information achieved with the lowest possible radiation dose. Exposure to ionising radiation can lead to cancer or development of hereditary defects. These effects can be expected with a low probability. After administration of the maximum recommended activity of this product, the effective dose is about 4 mSv.

In pediatric population (aged less than 18): it should be taken into consideration that the effective dose per MBq is higher in children than in adults (see section 11 Dosimetry)

Hypersensitivity reactions, including very rare (< 1/ 10,000) life-threatening anaphylaxis, have been reported following technetium (^{99m}Tc) medronate injection. These reactions have occurred 8 to 48 hours following the administration of medronate. Although variable in presentation, the reported cases have included one or more of generalized skin rash, oliguria and jaundice, vasculitis, signs consistent with erythema multiforme, and severe systemic illness consisting of nausea, headache, chills, cough, increased myalgias, and fever.

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 H_1 antagonist is helpful.

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

4.9 Overdose

In the event of the administration of a radiation overdose with technetium (^{99m}Tc) medronate injection, 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 frequent bladder voiding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals; skeleton; Technetium [^{99m}Tc] compounds, ATC code: V09B A02

When administered in usual doses Medronate DRAXIMAGE 10 mg shows no pharmacodynamic effects detectable clinically or/and analytically.

5.2 Pharmacokinetic properties

In the first 3 minutes after injection of technetium (^{99m}Tc) medronate injection, 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}Tc) medronate injection complex from a protein bound complex.

About 50% of the activity 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 activity 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 retention of 31.6 ± 5% is reported in healthy individuals, 38.2 ± 7% in those with extensive metastases, 49 ± 11% in primary hyper-parathyroidism and 45% in osteoporosis.

5.3 Preclinical safety data

Adverse events in animals after intravenous administration of medronate complex were only observed at doses sufficiently in excess of therapeutic doses in humans. Repeated administration of very high doses of diphosphonates can cause mineralization disorders. Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

p-Aminobenzoic acid
Stannous Chloride Dihydrate
Hydrochloric acid 1N (for pH adjustment)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

The technetium-^{99m} labelling reaction involved in preparing ^{99m}Tc-methylene diphosphonate complex depends on the maintenance of some tin in the divalent state. The presence of oxidating compounds in the pertechnate (^{99m}Tc) solution may adversely affect labeling.

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

6.3 Shelf life

2 years
After reconstitution: 12 hours

6.4 Special precautions for storage

Lyophilized product: Do not refrigerate or freeze.
Reconstituted product: Do not store above 25°C. Do not refrigerate or freeze.
Storage should be in accordance with national regulations for radioactive material.

The medicinal product should not come into contact with air.

6.5 Nature and contents of container

One vial contains 13.33 mg of powder.

10 ml Type 1 multidose glass vial closed with a butyl rubber stopper Type I. Medronate DRAXIMAGE 10 mg is supplied as 5, 10, 30 or 100 vials in a carton.

Not all pack size may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

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

7 MARKETING AUTHORISATION HOLDER

DRAXIMAGE (UK) Limited
5 Old Bailey, 2nd floor, London, EC4M 7BA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1419/2/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 28th March 2008

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY

The effective dose (E) of technetium (^{99m}Tc) medronate injection is 0.00619 mSv/MBq for females and 0.00475 mSv/MBq for males. The usual adult activity of 8 MBq/kg in a 70-kg female will result in an effective dose of 3.5 mSv; in an 80-kg male, it will result in an effective dose of 3.0 mSv.

Adult Effective Dose

	Dose (MBq/kg)	E (mSv/MBq)	Weight	E (mSv)
Woman	8	0.00619	70	3.47
Man	8	0.00475	80	3.04

Effective Dose (mSv/MBq) for children

0	*1 y*	*5 y*	*10 y*	*15 y*
0.0631	0.0263	0.0142	0.00904	0.0059

The effective dose per MBq will be higher in patients with reduced renal function and in patients with high bone uptake.

The target organ is the bone surface (0.063 mGy/MBq). For an administered activity of 600 MBq, the radiation dose to the bone surface is 37.8 mGy.

The critical organ is the bladder wall (0.048 mGy/MBq). For an administered activity of 600 MBq, the radiation dose to the bladder wall is 28.8 mGy.

The table below shows the dosimetry as calculated according to Publication 80 of the ICRP (International 1999)

Absorbed radiation doses: ^{99m}Tc-phosphate and phosphonate (mGy / MBq)

Organ	Absorbed dose per unit activity administered (mGy/MBq) Adult	15 years	10 years	5 years	1 years
Adrenals	0.0021	0.0027	0.0039	0.0058	0.011
Bladder wall	0.048	0.060	0.088	0.073	0.13
Bone surfaces	0.063	0.082	0.13	0.22	0.53
Brain	0.0017	0.0021	0.0028	0.0043	0.0061
Breast	0.00071	0.00089	0.0014	0.022	0.0042
Gall Bladder	0.0014	0.0019	0.0035	0.0042	0.0067
GI tract					
Stomach wall	0.0012	0.0018	0.0025	0.0035	0.0066
Small intestine	0.0023	0.0029	0.0044	0.0053	0.0095
Colon	0.0027	0.0034	0.0053	0.0061	0.011
Upper large intestine	0.0019	0.0024	0.0039	0.0051	0.0089
Lower large intestine	0.0038	0.0047	0.0072	0.0075	0.013
Heart	0.0012	0.0016	0.0023	0.0034	0.0060
Kidneys	0.0073	0.0088	0.012	0.018	0.032
Liver	0.0012	0.0016	0.0025	0.0036	0.0066
Lungs	0.0013	0.0016	0.0024	0.0036	0.0068
Muscles	0.0019	0.0023	0.0034	0.0044	0.0079
Oesophagus	0.0010	0.0013	0.0019	0.0030	0.0053
Ovaries	0.0036	0.0046	0.0066	0.0070	0.012
Pancreas	0.0016	0.0020	0.0031	0.0045	0.0082
Red Marrow	0.0092	0.01	0.017	0.033	0.067
Skin	0.0010	0.0013	0.0020	0.0029	0.0055
Spleen	0.0014	0.0018	0.0028	0.0045	0.0079
Testes	0.0024	0.0033	0.0055	0.0058	0.011
Thymus	0.0010	0.0013	0.0019	0.0030	0.0053
Thyroid	0.0013	0.0016	0.0023	0.0035	0.0056
Uterus	0.0063	0.0076	0.012	0.011	0.018
Remaining organ	0.0019	0.0023	0.0034	0.0045	0.0079
Effective dose (mSv/MBq)	**0.0057**	**0.0070**	**0.0110**	**0.0140**	**0.0270**

For Medronate DRAXIMAGE, the effective dose from the administration of 500 MBq technetium (^{99m}Tc) medronate is 2.85 mSv (for an individual weighing 70 kg).

The radiation dose to the target organ, bone surface, is 31.5 mGy/500 MBq.

For this activity of 500 MBq, the radiation doses delivered to the target organ (bone surfaces) is 3.15 31.5 mGy/500 MBq and the typical radiation dose to the critical organ, the bladder wall is 24.0 mGy/500 MBq

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Instructions for use

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure by use of suitable shielding. Use waterproof gloves during the following preparation procedure.

Before reconstituting a vial, it should be inspected for cracks and/or a melted plug or any other indication that the integrity of the pressure differential (inside/outside the vial) has been lost.

The medicinal product should not come into contact with air.

To prepare Technetium technetium ($^{99mTc)}$ medronate injection:

a) Remove the protective disc from a reaction vial and swab the closure with either an alcohol swab or a suitable bacteriostatic agent.

b) Place the reaction vial in a suitable lead vial shield (minimum wall thickness 1/8 inch) which has a fitted lead cap. Obtain 2 to 10 mLof sterile, non-pyrogenic sodium pertechnetate 99mTc injection Ph. Eur. using a shielded syringe.

c) Using a shielded syringe, aseptically introduce 740 to 18500 MBq (20 to 500 mCi) of sodium pertechnetate (99mTc) to a reaction vial. Sodium pertechnetate 99mTc solutions containing an oxidizing agent are not suitable for use.

d) Place the lead cap on the reaction vial shield and swirl the shielded reaction vial until the contents are completely dissolved. The solution must be clear and free of particulate matter before proceeding.

e) Assay the product in a suitable calibrator, record the radioassay information on the label with radiation warning symbol, and apply it to the reaction vial.

f) The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochemical purity should not be less than 95%.

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

h) Do not keep the labelled product above 25°C, in the refrigerator or the freezer. Use the labelled product within 12 hours. It should also be stored during its life in a suitable lead shield.

The pH of the solution is 6.5 to 7.5.

Method for control of radiochemical purity

The following procedure describes a series of simple steps for running chromatograms. Steps h and i describe 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

Solvant A: 136 mg/mL sodium acetate for determination of reduced technetium

Solvant B: Methylethylketon for determination of pertechnetate

a) Add 1 mLof the required solvent to an 18 mm x 150 mm test tube. Stopper the test tube and allow the atmosphere to equilibrate for 1 minute.

b) 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 mLtuberculin 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 microlitres disposable micropipette (e.g. Fisher Scientific 21-164-2D) can also be used to dispense 0.02 mL.

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

d) 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.

e) When the solvent front has climbed to the top of the strip, remove it with a 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.

f) In the sodium acetate (136 mg/mL) system, reduced TcO_2 stays at the origin or Rf = 0, while the bound and free technetium TcO4- move to the front (Rf = 0.85-1.0).

g) In the methylethylketon system, the bound and reduced fractions stay at the origin while free pertechnetate TcO4- migrates to the front (Rf = 0.85-1.0).

h) Method A - Determination of reduced technetium, using sodium acetate (136 mg/mL) 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 . Count the pieces in a suitable counter and determine the percentage of reduced technetium according to the following formula

$$\text{Percent } TcO_2 = \frac{\text{Counts in Part I} \quad X \quad 100}{\text{Counts in Part I} +}$$

i) Method B - Determination of pertechnetate, using methylethylketon:

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

$$\text{Percent } TcO_4^- = \frac{\text{Counts in Part IV} \quad X \quad 100}{\text{Counts in I} + \text{Part IV}}$$

NOTE: THE STRIPS ARE CUT IN DIFFERENT POSITIONS FOR METHODS A AND B.

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

$$\text{Percent Chelated Tc} = 100 - \%TcO_4^- - \%TcO_2$$

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

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. Radioactive waste must be disposed of in conformity with the relevant national and international regulations.