Radpharm HDP sodium oxidronate 3.15mg kit for the preparation of technetium (^{99m}Tc) oxidronate for injection

AUST R 160732

PRODUCT INFORMATION

NAME OF THE MEDICINE

Sodium Oxidronate

Chemical Name

Hydroxymethylenediphosphonate disodium salt (HDP)

Molecular Formula

$CH_4Na_2O_7P_2$

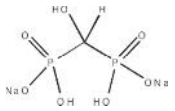
Molecular Weight

235.97

CAS Number

14255-61-9

Chemical Structure



DESCRIPTION

Radpharm HDP is supplied as sterile, pyrogen free, lyophilised powder, under nitrogen in borosilicate Type 1 glass 10mL vial for intravenous injection following reconstitution with non-pyrogenic 99mTc as pertechnetate sodium ($^{99m}TcO_4^-$).

The reconstituted product is a clear, colourless liquid.

Each 10mL tinted vial contains: Sodium oxidronate 3.15mg as an active ingredient; Stannous chloride dihydrate 0.297mg, Gentisic acid 0.84mg and Sodium chloride 29mg as excipients.

Radpharm HDP contains no antimicrobial preservatives.

Physical Characteristics of Technetium-99m

Technetium 99m, with a physical half life of 6 hours, decays by isomeric transition to technetium-99. Photons associated with this transition that are useful for detection and imaging studies are listed in the tables below, followed by the physical decay chart for Technetium-99[1].

Table 1: Principal Radiation Emission Data

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

Table 2: Physical Decay Chart for Technetium-99m

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 Technetium-99m is 0.19mGy/MBq-h at 1cm. The first half value thickness of lead (Pb) for Technetium-99m is 0.2mm. Attenuation by lead is given in Table 3.

Table 3: Radiation Attenuation by Lead Shielding

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

PHARMACOLOGY

Pharmacological Actions

Skeletal uptake of Sodium Oxidronate appears to be related to bone metabolic activity and skeletal blood flow. The exact mechanism of localisation of Technetium [^{99m}Tc] Sodium Oxidronate in bone is not entirely known. It is hypothesised that uptake occurs via chemisorption primarily in the mineral phase of bone, with insignificant binding to the organic matrix. Technetium [^{99m}Tc] Sodium Oxidronate demonstrates specific affinity for areas of altered osteogenesis.

Pharmacokinetics

After intravenous administration, Technetium [^{99m}Tc] Sodium Oxidronate is rapidly distributed in and cleared from blood with approximately 50% of the injected dose localizing in bone and less than 4% remaining in circulation at three hours post injection. The major pathway of elimination of Technetium [^{99m}Tc] Sodium Oxidronate via the kidneys. At 24 hours the percentage cumulative activity excreted in urine is 75% in patients with normal renal function.

INDICATIONS

Technetium [^{99m}Tc] Sodium Oxidronate may be used as a skeletal imaging agent to delineate areas of altered osteogenesis in adult patients.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General

This class of compounds is known to complex cations such as calcium. Particular caution should be used with patients who have, or who may be predisposed to hypocalcemia (alkalosis).

The content of the kit are not radioactive. However, after sodium pertechnetate [^{99m}Tc] is added, adequate shielding of the final preparation must be maintained to minimize radiation exposure to occupational workers and patients.

Adequate hydration of the patient is recommended before and after examination to promote urinary flow. Also, urination is recommended as often as possible for 4 to 6 hours after the examination to reduce bladder exposure radiation.

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 dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (EDE) is less than 20mSv. Higher doses may be justified in some clinical circumstances.

Radiopharmaceuticals should only be used by physicians who are qualified by specific training in the safe use and handling of radionuclides.

Contents of the vial are intended only for use in the preparation of Technetium [^{99m}Tc] Sodium Oxidronate.

The radioactivity of the dose should be checked with a suitable instrument immediately prior to administration.

Disposal of all radioactive wastes should be carried out in accordance with the NHMRC "Code of Practice for the Disposal of Radioactive Wastes by the User" (1985).

Use in Patients with Impaired Renal Function

Patients with renal impairment or suffering from renal obstructions may give rise to a higher level of radiation exposure.

Use in Patients with Impaired Gastrointestinal Tract

Patients with gastrointestinal tract obstructions may give rise to a higher level of radiation exposure.

Women of childbearing age

Examinations using radiopharmaceuticals, especially those elective in nature, of women of childbearing capability, should be performed during the first 10 days following the onset of menses.

Use in Pregnancy

Women of reproductive age presenting for a Technetium [^{99m}Tc] Sodium Oxidronate study must be carefully interviewed to assess the likelihood of pregnancy. Irradiation of a foetus should be avoided whenever possible. Technetium [^{99m}Tc] Sodium Oxidronate should only be given to a pregnant woman if in the judgement of the treating physician the expected benefits outweigh the potential hazards. In cases where medical radiation exposure is justified and considered necessary, the practice should be optimized in order to both minimize the dose to the foetus and achieve a diagnostic study[2]. It is suggested that in order to achieve this, the use of smaller administered activities and longer imaging times, together with maternal hydration and frequent voiding will lead to a reduced dose to the foetus and a clinically diagnostic study. If clinically justifiable a slight postponement of the examination to a later stage of the pregnancy will also lead to a reduced dose to the foetus[2]. It should be noted that contamination from radionuclide and radiopharmaceutical impurities can considerably affect the amount of activity transferred to the foetus. Therefore, in order to avoid unjustified doses to the foetus, attention should be paid to quality control of radiopharmaceutical compounds administered[2].

Use During Lactation

Technetium [^{99m}Tc] Sodium Oxidronate is excreted in human milk. If the patient is breast-feeding following administration of Technetium [^{99m}Tc] Sodium Oxidronate a procedure should be in place to ensure that the infant will receive a total effective dose of no more than 1mSv[3]. In order to achieve this it is recommended that the patient express and store milk prior to administration of Technetium [^{99m}Tc] Sodium Oxidronate. Following administration of Technetium [^{99m}Tc] Sodium Oxidronate a 1 hour interruption to breast feeding and reduced contact with the infant is recommended[3]. During this period of interruption it is recommended that the mother express and discard at least one fraction of milk. Where sample counting facilities are available it may be preferable to directly measure the concentration of the radionuclide in the breast milk to determine the time at which breast-feeding can resume[3]. To ensure the infant receives a total effective dose of no more than 1mSv breast feeding may resume when the milk activity concentration falls on or below 1kBq/mL[3]. It should be noted that contamination from radionuclide and radiopharmaceutical impurities can considerably affect the amount of activity in the milk. Therefore, attention should be paid to quality control of radiopharmaceutical compounds administered, in order to avoid unjustified doses to the infant[2].

Carcinogenesis, Mutagenesis and Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic or mutagenic potential effects on the foetus.

INTERACTIONS WITH OTHER MEDICINES

Calcium Gluconate and Calcium Chloride

Caution must be taken in administering Technetium [^{99m}Tc] Sodium Oxidronate to patients with calcium gluconate and calcium chloride for hypocalcemia (i.e.

alkalosis) as oxidronate is known to complex with calcium cations.

ADVERSE EFFECTS

Adverse reactions to Technetium [^{99m}Tc] Sodium Oxidronate are rare. However some hypersensitivity reactions, dermatological manifestations (erythema) and diaphoresis, as well as nausea, vomiting and heartburn have been infrequently associated with Technetium [^{99m}Tc] Oxidronate administration[4].

Hypersensitivity and allergic reactions can often be treated with a non-selective histamine H1 antagonist.

Body as a Whole: hypersensitivity reactions.

Digestive: nausea, vomiting, heartburn.

Skin and Appendages: dermatological manifestations (erythema), injection site inflammation/reaction.

DOSAGE AND ADMINISTRATION

Adult: The recommended intravenous dose of Technetium [^{99m}Tc] Sodium Oxidronate for the average adult patient (70kg) is 555MBq, with a minimum administered activity of 370MBq and maximum administered activity is 740MBq. The administered dose of Sodium Oxidronate should not exceed 0.05mg/kg.

General Instructions: The administered dose of Sodium Oxidronate is between 0.001-0.05mg/kg. The ideal administered dose of Sodium Oxidronate is 0.005mg/kg. The radioactivity of each dose should be measured by an appropriate radiation calibration system immediately prior to administration. The dose should be administered intravenously by slow injection. For optimal results bone imaging should be performed 1-4 hours post-injection.

Radiation Dosimetry

The estimated absorbed radiation doses and effective doses from an intravenous administration of Technetium [^{99m}Tc] Sodium Oxidronate are presented in Table 4.

Table 4: Estimated absorbed radiation dose per unit administered activity[5]

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	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	2.1E03	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-03	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	1.3E-03	3.4E-03	4.5E-03	7.9E-03
Effective dose (mSv/MBq)	5.7E-03	7.0E-03	1.1E-02	1.4E-02	2.7E-02

Procedural Precautions

1. Visually inspect vial, ensure vial contains product (dry white powder).
2. Waterproof gloves should be worn, and aseptic technique adhered to during the preparation of Technetium [^{99m}Tc] Sodium Oxidronate and for all subsequent dose withdrawals.
3. As Radpharm HDP is a multidose kit, precaution must be taken in order to prevent contamination of the vial. If there is more than one patient being administered Technetium [^{99m}Tc] Sodium Oxidronate from the same Radpharm HDP vial on a single day all doses must be withdrawn from the reconstituted vial using aseptic technique and a shielded syringe prior to the first dose administration.
4. Usual precautions regarding radioprotection should be implemented.
5. Solutions of Sodium Pertechnetate [^{99m}Tc] which contain oxidizing agents should not be used.

Dose Preparation Procedure

Note: If the Radpharm HDP vial requires reconstitution for a single adult patient or paediatric patients take extra care in ensuring that no more than 0.05mg/kg of Sodium Oxidronate is administered.

1. Remove the protective disc from the Radpharm HDP vial and swab the rubber stopper with an appropriate antiseptic. Allow rubber stopper to dry completely.
2. Place the Radpharm HDP vial in a suitable lead vial shield with a minimum wall thickness of 3mm and a fitted lead cap.
3. Using aseptic technique and a shielded syringe withdraw 3mL to 6mL of sterile non-pyrogenic Sodium Pertechnetate [^{99m}Tc] eluted from a Technetium-99m generator. The recommended activity range of Sodium Pertechnetate [^{99m}Tc] to be added to the Radpharm HDP vial is 2 to 11 GBq.
4. Using aseptic technique and a shielded syringe add the Sodium Pertechnetate [^{99m}Tc] to the Radpharm HDP vial. Mix by gentle inversion for approximately 30 seconds to ensure complete dissolution.
5. The resulting solution should be clear and free of particulate matter. If not, the vial should not be used. Affix a label to the lead vial shield recording the date and time prepared and the activity and volume of Sodium Pertechnetate [^{99m}Tc] added to the Radpharm HDP vial.
6. The radiochemical purity of the reconstituted solution must be checked prior to administration to the patient using the current British Pharmacopeia Medronate method.
7. Withdraw each patient dose of Technetium [^{99m}Tc] Sodium Oxidronate using aseptic technique and a shielded syringe. If there is more than one patient being administered Technetium [^{99m}Tc] Sodium Oxidronate from the same kit, all doses must be withdrawn from the reconstituted vial prior to the first dose administration.
8. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The Technetium [^{99m}Tc] Sodium Oxidronate solution is stable at room temperature and may be used up to 8 hours after preparation.

Note: In order to reduce the radiation dose to the bladder and other organs, the patient should be encouraged to drink and void as frequently as possible for a period of 4 to 6 hours after the administration of Technetium [^{99m}Tc] Sodium Oxidronate.

OVERDOSAGE

In the event of the administration of a radiation overdose with Technetium [^{99m}Tc] Sodium Oxidronate 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.

PRESENTATION AND STORAGE CONDITIONS

Radpharm HDP is supplied as a carton of sterile, pyrogen free, under nitrogen, multidose, tinted 10mL vials enclosed in a carton.

Radpharm HDP is available in 10 x 10mL vials and 30 x 10mL vial cartons.

Radpharm HDP vials may be stored at room temperature, below 25°C before reconstitution.

Reconstituted Radpharm HDP vials may be stored at room temperature, below 25°C.

Reconstituted shelf life of Radpharm HDP is 8 hours. Discard any unused portions.

The shelf life is 12 months from the date of manufacture. The expiry date is stated on the vial and carton.

NAME AND ADDRESS OF THE SPONSOR

RADPHARM
SCIENTIFIC

53-59 Oatley Court
Belconnen ACT 2617
Ph: +61 2 6251 6533

DATE OF APPROVAL

Date of First Inclusion in the Australian Register of Therapeutic Goods (The ARTG): 15 August 2011

Date of Most Recent Amendment: 5 February 2016

REFERENCES

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