AUSTRALIAN PRODUCT INFORMATION

PENTASTAN KIT (PENTETIC ACID) MULTI DOSE VIALS

1 NAME OF THE MEDICINE

PENTASTAN Kit for preparation of Technetium (^{99m}Tc) pentetate injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 13.25 mg of Na-DTPA i.e. sodium diethylenetriaminepentaacetate monohydrate (equivalent to 10 mg of pentetic acid), 800 micrograms (µg) of stannous chloride, di-hydrate and 7.10 mg of sodium chloride.

The contents of the vial is freeze-dried solid and sealed in nitrogen atmosphere.
As supplied the product is sterile and pyrogen free; it contains no antimicrobial preservative.

The product is designed for diagnostic use only. Administration after reconstitution with sterile sodium pertechnetate solution is by intravenous injection.

Physical Characteristics of ^{99m}Tc

Technetium-99m, with a physical half-life of six hours, decays by isomeric transition to technetium-99. Photons associated with this transition, useful for detection and imaging studies is listed in Table 1. Decay profile of ^{99m}Tc is given in Table 2.

Table 1:

Principal Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	87.2	140.5

Table 2: Physical Decay Profile of ^{99m}Tc.

Hours	Fraction Remaining	Hours	Fraction Remaining
	1.000	5	0.562
1	0.891	6	0.501
2	0.794	7	0.447
3	0.708	8	0.398
4	0.631		

External Radiation

The specific gamma ray constant for ^{99m}Tc is 0.19mGy per MBq^{-h} at 1cm. The first half value thickness of lead for ^{99m}Tc is 0.2mm. A range of values for the relative attenuation of the radiation emitted by ^{99m}Tc resulting from the interposition of various thicknesses of lead is given in Table 3.

Table 3: Relative attenuation of radiation emitted by ^{99m}Tc at various Lead (Pb) shield thickness.

Shield Thickness (mm Pb)	Coefficient of Attenuation (approx.)
0.2	0.5
0.95	0.1
1.8	0.01
2.7	0.001
3.6	0.0001

For full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
Sterile, pyrogen free, freeze-dried solid, powder for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Pentastan Kit after radiolabelling to produce ^{99m}Tc-Pentetate may be used to perform kidney imaging, brain imaging, to assess renal perfusion and to estimate glomerular filtration rate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Each vial contains Pentetic Acid intended for 2 or more doses.

(a) Pentastan kit is designed for labelling with technetium-99m (as sodium pertechnetate, ^{99m}Tc) obtained from Mo-99/Tc-99m sterile generators (such as ANSTO's GENTECH generator or equivalent generators from other manufacturers). The labelling procedure should be performed in the workstation providing protection against ionizing radiation and using aseptic techniques that ensures sterility of the preparation.

Radiolabelling procedure for the preparation of ^{99m}Tc-Pentetate Injection solution using the Pentastan Kit product is prepared for clinical use is given below:

Labelling procedure:

- Place the kit vial containing the lyophilisate in an appropriate radioprotective shield.
- Using a syringe inject (by piercing the rubber stopper) about 5 mL of eluate of sodium pertechnetate (eluate with desired activity pre-diluted with sterile saline) into freeze-dried Pentastan Kit vial.
- Using the same syringe relieve the excess pressure in the vial by withdrawing the volume of gas equivalent to the volume of sodium pertechnetate ^{99m}Tc solution added.
- Shake the contents of the vial until complete dissolution of the freeze-dried solid (about 2 min.). Keep the vial in the shield all the time.
- The resultant solution is a ready for use as ^{99m}Tc-Pentetate solution for injection.
- It is recommended that reconstituted ^{99m}Tc-Pentetate Injection solution should be used within 6 hours after completion of the labelling procedure.

(b) Recommended activity:

The suggested dose for a normal (70kg) adult is:

- Brain Scan: 400-800 MBq
- Renal Scan: 200 MBq

For children, the dose should be reduced to that appropriate to the patient's weight.

The patient dose should be measured with a suitable radioactivity calibrator immediately before administration. Radiochemical purity should be checked prior to administration. Shielding should be used when preparing ^{99m}Tc-Pentetate solution.

(c) Determination of Radiochemical Purity:

The radiochemical purity should be checked prior to administration. It can be measured by Thin Layer Chromatography – using two chromatographic systems according to Ph. Eur. Monograph 0642.

Impurity A: [^{99m}Tc] technetium in colloidal form

(i) TLC silica gel plate: Use silica gel as the coating substance on a glass-fibre sheet, previously heated at 110 °C for 10 min.

(ii) Mobile phase: 9 g/L solution of sodium chloride

(iii) Application: 5-10 µL of the examined solution about 1.5 cm from the bottom of a 1.5 cm x 12 cm chromatographic plate

(iv) Development: Immediately, until the solvent front moves to about 4/5 of the plate in about 10 min.

(v) Drying: In the air

(vi) Detection: Suitable detector to determine the distribution of radioactivity.

(vii) Retardation factors:

- Impurity A = 0.0 to 0.1 (Rf value)
- [^{99m}Tc] technetium pentetate and impurity B = 0.9 to 1.0 (Rf value).

Impurity B: [^{99m}Tc] pertechnetate ion

(i) TLC silica gel plate: Use silica gel as the coating substance on a glass-fibre sheet, previously heated at 110 °C for 10 min.

(ii) Mobile phase: methyl ethyl ketone

(iii) Application: 5-10 µL of the examined solution about 1.5 cm from the bottom of a 1.5 cm x 12 cm chromatographic plate

(iv) Development: Immediately, until the solvent front moves to about 4/5 of the plate in about 10 min.

(v) Drying: In the air

(vi) Detection: Suitable detector to determine the distribution of radioactivity.

(vii) Retardation factors:

- [^{99m}Tc] technetium pentetate and Impurity A = 0.0 to 0.1 (Rf value)
- Impurity B = 0.9 to 1.0 (Rf value)

Limit - Sum of impurities A and B:

Maximum 5.0 per cent of the radioactivity due to technetium-99m in the chromatograms obtained in tests for Impurity A and B.

Radiation Dosimetry

The estimated radiation absorbed dose to various organs from an intravenous injection of ^{99m}Tc-Pentetate in patients with normal and abnormal renal function is given in Tables 4 and Table 5 respectively. This data have been taken from "ICRP publication 128, Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances"; p.154-157.

Table 4: Absorbed dose per unit activity administered (mGy MBq^{-1}) in Patients with normal renal function.

Organ	*Absorbed dose per unit activity administered (mGy MBq^{-1})				
	Adult	15 years	10 years	5 years	1 year
Adrenals	1.4E_03	1.8E_03	2.7E_03	4.0E_03	7.2E_03
Bone surfaces	2.4E_03	2.9E_03	4.3E_03	6.1E_03	1.0E_02
Brain	8.6E_04	1.1E_03	1.7E_03	2.8E_03	4.9E_03
Breast	7.2E_04	9.2E_04	1.3E_03	2.2E_03	4.1E_03
Gallbladder wall	1.5E_03	2.1E_03	3.8E_03	5.0E_03	6.1E_03
Gastrointestinal tract -					
Stomach wall	1.3E_03	1.7E_03	2.8E_03	4.0E_03	6.8E_03
Small intestine wall	2.5E_03	3.1E_03	4.9E_03	7.0E_03	1.0E_02
Colon wall	3.1E_03	3.9E_03	6.0E_03	8.1E_03	1.1E_02
(Upper large intestine wall	2.1E_03	2.8E_03	4.3E_03	6.5E_03	9.2E_03)
(Lower large intestine wall	4.3E_03	5.4E_03	8.2E_03	1.0E_02	1.3E_02)
Heart wall	1.2E_03	1.5E_03	2.2E_03	3.3E_03	5.9E_03
Kidneys	4.4E_03	5.3E_03	7.5E_03	1.1E_02	1.8E_02
Liver	1.2E_03	1.6E_03	2.5E_03	3.8E_03	6.4E_03
Lungs	1.0E_03	1.3E_03	2.0E_03	3.0E_03	5.5E_03
Muscles	1.6E_03	2.0E_03	3.0E_03	4.3E_03	6.8E_03
Oesophagus	1.0E_03	1.3E_03	1.9E_03	3.0E_03	5.4E_03
Ovaries	4.2E_03	5.3E_03	7.7E_03	1.0E_02	1.3E_02
Pancreas	1.4E_03	1.8E_03	2.8E_03	4.3E_03	7.4E_03
Red marrow	1.5E_03	1.8E_03	2.7E_03	3.7E_03	5.7E_03
Skin	8.7E_04	1.0E_03	1.7E_03	2.6E_03	4.4E_03
Spleen	1.3E_03	1.6E_03	2.6E_03	3.9E_03	6.8E_03
Testes	2.9E_03	4.0E_03	6.8E_03	9.4E_03	1.3E_02
Thymus	1.0E_03	1.3E_03	1.9E_03	3.0E_03	5.4E_03
Thyroid	1.0E_03	1.3E_03	2.1E_03	3.3E_03	6.0E_03
Urinary bladder wall	6.2E_02	7.8E_02	1.1E_01	1.5E_01	1.7E_01
Uterus	7.9E_03	9.6E_03	1.5E_02	1.8E_02	2.2E_02
Remaining organs	1.7E_03	2.1E_03	3.0E_03	4.2E_03	6.6E_03
Effective dose (mSv MBq^{-1})	4.9E_03	6.3E_03	9.4E_03	1.2E_02	1.6E_02

- *Physical half-life of ^{99m}Tc is 6.01 h.*
- *ICRP publication 128, Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances*

* *Dose calculations have been performed for adults and 15-, 10-, 5-, and 1- year-old children.*

Table 5: Absorbed dose per unit activity administered (mGy MBq^{-1}) in Patients with abnormal renal function.

Organ	*Absorbed dose per unit activity administered (mGy MBq^{-1})				
	Adult	15 years	10 years	5 years	1 year
Adrenals	4.1E_03	5.1E_03	7.6E_03	1.1E_02	2.1E_02
Bone surfaces	6.0E_03	7.1E_03	1.1E_02	1.5E_02	2.8E_02
Brain	2.8E_03	3.5E_03	5.7E_03	9.1E_03	1.6E_02
Breast	2.3E_03	3.0E_03	4.2E_03	6.8E_03	1.3E_02
Gallbladder wall	4.2E_03	5.7E_03	9.2E_03	1.3E_02	1.6E_02
Gastrointestinal tract -					
Stomach wall	3.8E_03	5.0E_03	7.9E_03	1.1E_02	1.9E_02
Small intestine wall	4.5E_03	5.6E_03	8.5E_03	1.3E_02	2.2E_02
Colon wall	4.5E_03	5.8E_03	8.7E_03	1.3E_02	2.2E_02
(Upper large intestine wall	4.3E_03	5.6E_03	8.1E_03	1.3E_02	2.1E_02)
(Lower large intestine wall	4.9E_03	6.1E_03	9.5E_03	1.3E_02	2.3E_02)
Heart wall	3.7E_03	4.7E_03	7.0E_03	1.0E_02	1.8E_02
Kidneys	7.7E_03	9.2E_03	1.3E_02	1.9E_02	3.2E_02
Liver	3.7E_03	4.6E_03	7.1E_03	1.1E_02	1.9E_02
Lungs	3.3E_03	4.2E_03	6.2E_03	9.5E_03	1.7E_02
Muscles	3.2E_03	4.0E_03	6.1E_03	9.1E_03	1.7E_02
Oesophagus	3.3E_03	4.2E_03	6.2E_03	9.6E_03	1.7E_02
Ovaries	5.0E_03	6.2E_03	9.2E_03	1.4E_02	2.3E_02
Pancreas	4.3E_03	5.3E_03	8.0E_03	1.2E_02	2.1E_02
Red marrow	3.4E_03	4.2E_03	6.4E_03	9.3E_03	1.6E_02
Skin	2.2E_03	2.6E_03	4.2E_03	6.7E_03	1.2E_02
Spleen	3.8E_03	4.7E_03	7.3E_03	1.1E_02	1.9E_02
Testes	3.5E_03	4.5E_03	6.9E_03	1.0E_02	1.8E_02
Thymus	3.3E_03	4.2E_03	6.2E_03	9.6E_03	1.7E_02
Thyroid	3.4E_03	4.2E_03	6.7E_03	1.1E_02	1.9E_02
Urinary bladder wall	2.1E_02	2.7E_02	3.9E_02	5.0E_02	6.6E_02
Uterus	6.1E_03	7.4E_03	1.1E_02	1.6E_02	2.5E_02
Remaining organs	3.3E_03	4.1E_03	6.3E_03	9.7E_03	1.7E_02
Effective dose (mSv MBq^{-1})	4.6E_03	5.8E_03	8.7E_03	1.3E_02	2.1E_02

- *Physical half-life of ^{99m}Tc is 6.01 h.*
- *The urinary bladder wall contributes up to 57% of the effective dose.*
- *ICRP publication 128, Radiation Dose to Patients from Radiopharmaceuticals: a Compendium of Current Information Related to Frequently Used Substances.*

* *Dose calculations have been performed for adults and 15-, 10-, 5-, and 1- year-old children.*

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Radiopharmaceuticals should only be used by physicians who are qualified and licensed to handle radioactive. Contents of the kit are intended only for use in the preparation of technetium ^{99m}Tc-Pentetate injection. They should not be administered directly to the patient. Solutions containing Sodium Pertechnetate with antioxidants should not be used. At time of administration the solution should be crystal clear.

Dose Handling

Radiation exposure to clinical personnel must be minimised. Care and appropriate safety measures should always be used.

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

Pentastan Kit vial contains no bactericide. Aseptic techniques must be used at all times when handling the product.

Patient Care

Care should be taken to minimise unwanted radiation exposure to patients, consistent with proper patient management

In order to reduce radiation dose to the bladder the patient should be encouraged to drink fluids and to void (empty bladder) as frequently as possible following the administration of the radiopharmaceutical for a period of four to six hours.

Patients with renal impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Use in the elderly

No specific data in elderly are available

Paediatric use

This radiopharmaceutical should generally not be administered to persons under 18 years of age unless the benefits to be gained outweigh the potential hazards. Refer to section 4.2 (b)

For children, the dose should be reduced to that appropriate to the patients weight.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No data was available at time of registration of this product.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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 foetus.

Use in pregnancy

This radiopharmaceutical should not be administered to pregnant or nursing women unless the benefits to be gained outweigh the potential hazards. Ideally, examination of a woman of childbearing capabilities should be performed only during the 10 days following the onset of menses.

Use in lactation

Technetium (^{99m}Tc) is excreted in human milk. If administered to a nursing mother, formula feeding must be substituted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

No adverse reactions have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at – h*ttp://www.tga.gov.au/reporting-problems*.

4.9 OVERDOSE

In the event of the administration of a radiation overdose with Technetium (^{99m}Tc) pentetate 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.
For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Following intravenous injection, ^{99m}Tc-Pentetate is rapidly distributed throughout the extracellular fluid space, where it is promptly cleared from the body by glomerular filtration. There is minimal binding to the renal parenchyma.

^{99m}Tc-Pentetate tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. The agent does not accumulate in the choroid plexus.

Since medicine is excreted by glomerular filtration, the images of the kidneys obtained during the first few minutes after injection show the vascular pool within the kidney. Subsequent images represent radioactivity in both the collecting system and the renal pelvis.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

No data was available at time of registration of this product.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium Chloride, BP
Stannous Chloride Dihydrate, BP

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging' under this heading.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

- Pentastan Kit should be stored between 2-8°C (Refrigerate. Do not freeze).
- The reconstituted ^{99m}Tc-Pentetate should be stored below 8°C and is to be used within 6 hours of reconstitution.
- During transportation, Pentastan Kit can be handled / stored at up to up to 35°C (for not longer than 7 days).

6.5 NATURE AND CONTENTS OF CONTAINER

(i) Primary (vial): The primary container is a labelled 10mL colourless glass vial with a grey rubber bung and white centre tear crimp cap.

(ii) Secondary (outer carton): The glass vial is packed in a carton. Each carton box contains: 6 x Labelled vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Disposal of all radioactive wastes should be carried out in accordance with the *ARPANSA's "Code for the Disposal of Radioactive Waste by the User - Radiation Protection Series, C-6, September 2018".*
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

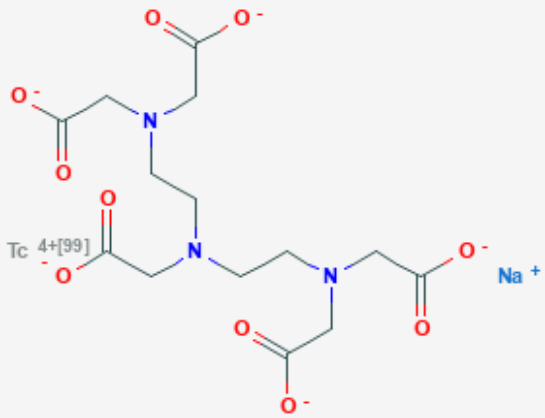
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Name: sodium;2-[bis[2[bis(carboxylatomethyl)amino]ethyl]amino]acetate;technetium-99m

Molecular Formula: $C_{14}H_{18}N_3NaO_{10}{}^{99m}Tc$

Structure:



CAS number: 65454-61-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled.

8 SPONSOR

ANSTO
New Illawarra Rd,
Lucas Heights
NSW 2234, Australia

Mailing address:
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Telephone: 1800 251 572
Facsimile: 02 9543 6511
E-mail: health@ansto.gov.au
Website: www.ansto.gov.au

Product Code:
10913

Australian Registration Number:
AUST R: 22926

9 DATE OF FIRST APPROVAL

15/10/1991

10 DATE OF REVISION

24 August 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	- Update to new PI format - Minor editorial updates
2	- Updated: • The contents of the vial to "freeze-dried solid" • "sealed in nitrogen atmosphere"
3	- Included "pharmaceutical form" information
4	- Included / updated: • Labelling procedure (section 4.2 - a) • "Radiochemical Purity' determination (section 4.2 – c) • Radiation Dosimetry section for "radiation absorbed dose of Technetium (^{99m}Tc) Pentastan" in tables 4 & 5 as per updated ICRP publication 128 • Contraindications (section 4.3) • Use in the elderly • Paediatric use • Effects on laboratory tests • Interactions with other medicines and other forms of interactions (section 4.5) • Effects on ability to drive and use machines (section 4.7) • Adverse effects (section 4.8) • Overdose (section 4.9)
6	- Included / updated • List of excipients (section 6.1) • Incompatibilities (section 6.2) • Shelf-life (section 6.3) • Special precautions for storage (section 6.4) • Nature and contents of container (section 6.5) • Special precautions for disposal (section 6.6) • Physiochemical properties (section 6.7)
7	- Included "medicine schedule (poisons standard)"
8	- Included "date of first approval"
9	- Included "date of revision"
N/A	- Included "summary table of changes"

Australian Government

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