Molybdenum [99Mo]/Technetium [99mTc] Sterile Generator

For the Production of Sodium Pertechnetate [99mTc] Injection (fission BP)

Description
The ANSTO Health Generator provides a means of obtaining a sterile, isotonic, additive and pyrogen free solution of Sodium Pertechnetate [99mTc] Injection (fission BP). The generator contains fission-product molybdenum-99 (99Mo) from which 99mTc is separated by elution into evacuated vials. The generator consists of a sealed glass vessel containing aluminium oxide. The 99Mo is firmly bound to the alumina and as a result, the eluted 99mTc contains negligible amounts of 99Mo. Over the life of the generator, an elution will provide a yield of approximately 90% of the theoretical amount of [99mTc] available from the 99Mo contained within the generator vessel.

Physical Characteristics
Technetium-99m, with a physical half-life of 6 hours, decays by isomeric transition to 99Tc. Photons associated with this transition which are useful for detection and imaging studies are listed in Table 1.

Table 1
<table>
<thead>
<tr>
<th>Principal Radiation</th>
<th>Mean % per Disintegration</th>
<th>Mean Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma-2</td>
<td>89.1</td>
<td>140.5</td>
</tr>
</tbody>
</table>


External Radiation
The specific gamma ray constant for 99mTc is 0.19mGy per MBq-h at 1cm. The first half value thickness of lead for 99mTc is 0.2mm. Attenuation by lead is given in the following table.

Table 2
<table>
<thead>
<tr>
<th>Shield Thicknesses mm Pb</th>
<th>Coefficient of Attenuation (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>0.95</td>
<td>10^-1</td>
</tr>
<tr>
<td>1.8</td>
<td>10^-2</td>
</tr>
<tr>
<td>2.7</td>
<td>10^-3</td>
</tr>
<tr>
<td>3.6</td>
<td>10^-4</td>
</tr>
</tbody>
</table>

Elution Behaviour
Molybdenum-99, with a half-life of 2.75 days, decays to 99mTc. The physical decay characteristics of 99Mo are such that 87.5% of its disintegrations form 99mTc. The activity of 99mTc available for elution from the generator will depend upon the time interval from the last elution but reaches a maximum approximately 23 hours after the previous elution which is equivalent to 87.6 percent of the 99Mo activity at that time. Table 3 shows the 99mTc activity for a given growth period following complete elution, relative to the 99Mo activity contained in the generator at the end of the growth period.

Table 3
<table>
<thead>
<tr>
<th>Growth Periods (hours)</th>
<th>99mTc:99Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.096</td>
</tr>
<tr>
<td>2</td>
<td>0.162</td>
</tr>
<tr>
<td>4</td>
<td>0.329</td>
</tr>
<tr>
<td>8</td>
<td>0.546</td>
</tr>
<tr>
<td>24</td>
<td>0.885</td>
</tr>
<tr>
<td>48</td>
<td>0.957</td>
</tr>
</tbody>
</table>

Table 4
<table>
<thead>
<tr>
<th>Physical Decay Chart 99Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

Table 5
<table>
<thead>
<tr>
<th>Physical Decay Chart 99mTc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
Pharmacology
No pharmacological activity has been observed in the range of doses administered for diagnostic purposes.

Pharmacokinetic Properties
The pertechnetate ion has similar biological distribution to iodide and perchlorate ions, concentrating temporarily in salivary glands, choroid plexus, stomach (gastric mucosa) and in the thyroid gland, from which it is released unchanged. The pertechnetate ion also tends to concentrate in areas with increased vascularisation or with abnormal vascular permeability, particularly when pre-treatment with blocking agents inhibits uptake in glandular structures.

Technetium - 99m is selectively excreted from the cerebrospinal fluid. Following intravenous administration, pertechnetate \([^{99m}\text{Tc}]\) is distributed throughout the vascular system from which it is cleared by three main mechanisms:

- **rapid removal**, depending on the diffusion equilibrium with interstitial fluid;
- **intermediate rate of removal**, depending on the concentration of the pertechnetate in glandular tissue, mainly thyroid, salivary and gastric fundus glands which have an ionic pump mechanism;
- **slow removal**, by glomerular filtration by the kidneys, dependent on rate of urinary excretion.

Plasma clearance has a half-life of approximately 3 hours. Excretion during the first 24 hours following administration is mainly urinary (~25%) with faecal excretion occurring over the next 48 hours. Approximately 50% of the administration activity is excreted within the first 50 hours.

When selective uptake of pertechnetate \([^{99m}\text{Tc}]\) in glandular structures is inhibited by the pre-administration of blocking agents, excretion follows the same pathways but there is a higher rate of renal clearance.

When pertechnetate \([^{99m}\text{Tc}]\) is administered in association with pretreatment with reducing agents such as stannous/medronate which cause a “stannous leading” of red blood cells, up to approximately 95% of the administered activity is taken up by the red blood cells where it becomes bound within the cells. Any unbound pertechnetate \([^{99m}\text{Tc}]\) is cleared by the kidneys. Radioactivity in the plasma normally constitutes less than 5% of the intravascular activity.

The fate of technetium-99m follows that of the labelled erythrocyte themselves and the activity is cleared very slowly. A small level of elution of activity from the circulating red cells is thought to occur.

Sodium pertechnetate injection may be reacted with a range of reagents (cold kits) to provide diagnostic agents for the imaging of specific organs.

Indications
Sodium pertechnetate \([^{99m}\text{Tc}]\) is used for scintigraphy, principally of the brain and thyroid. It can also be used to prepare various technetium-99m labelled injections for selective organ imaging especially of the liver, lung, bone and kidney.

Contraindications
Since Sodium Pertechnetate \([^{99m}\text{Tc}]\) is excreted through the kidneys and the gastrointestinal tract, its use in patients suffering obstructive pathology may give rise, to a higher level of radiation exposure.

Precautions
General
Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by a nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agency authorised to license the use of radionuclides.

Care should be taken to minimise radiation exposure to patients consistent with proper patient management. As with other radioactive drugs, Sodium Pertechnetate \([^{99m}\text{Tc}]\) must be handled with care and appropriate safety measures should be used to minimise radiation exposure to clinical personnel.

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 with caution in the following circumstances
Because the pertechnetate ion is concentrated in the thyroid gland, choroid plexus and salivary glands, a blocking dose of up to 1 gram of reagent grade potassium perchlorate in a suitable base of capsule may be given orally prior to the administration of Sodium pertechnetate \([^{99m}\text{Tc}]\) injection for brain scanning.

Patients who have had scans performed on them in the previous 6 weeks with agents containing tin may show distribution artefacts and/or poor quality images in a subsequent Sodium pertechnetate \([^{99m}\text{Tc}]\) brain scan as a result of uptake of pertechnetate by the red blood cells. The physician should give special consideration in such cases to an alternative agent, eg. \([^{99m}\text{Tc}]\):DTPA.

Check the following before use
Verification of the dose to be administered and patient identification is necessary prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoulouration prior to administration whenever solution or container permits.

At the time of administration the solution should be crystal clear and should not be used if it is cloudy or if it contains particulate matter.

Carcinogenesis, Mutagenesis, Impairment of 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
Direct administration of 800 MBq Sodium pertechnetate \([^{99m}\text{Tc}]\) to a patient results in an absorbed dose to the uterus of 6.5mGy. Following pretreatment of patients with a blocking agent, administration of 800 MBq Sodium pertechnetate \([^{99m}\text{Tc}]\) results in an absorbed dose to the uterus of 5.3 mGy.

Administration of 925 MBq \([^{99m}\text{Tc}]\):DTPA-labelled red blood cells results in an absorbed dose to the uterus of 4.3mGy. Doses above 0.5mGy should be regarded as a potential risk to the foetus.

Use in Lactation
As a general rule breast-feeding should not be undertaken when a patient is administered radioactive material.

If the administration is considered necessary, breast-feeding should be interrupted and the expressed feeds discarded.

Breast-feeding can be restarted when the activity level in the milk will not result in a radiation dose to the child greater than 1mSv.

Paediatric Use
Safety and effectiveness in children have not been established.

Interactions with other drugs
Drug interactions have been reported in brain scintigraphy where there can be increased uptake of \([^{99m}\text{Tc}]\) pertechnetate in the walls of cerebral ventricles as a result of methotrexate induced ventriculitis.

In abdominal imaging, drugs such as atropine, isoprenaline and analgesics can result in a delay in gastric emptying and redistribution of pertechnetate.
Adverse Reactions

The following adverse reactions have been reported following intravenous injection of Sodium pertechnetate $^{99m}$Tc:

- Hypersensitivity and Skin: urticaria, pruritus
- Cardiovascular: arrhythmia, vasodilation
- Body as a whole: facial oedema, coma

Dosage and Administration

Sodium Pertechnetate $^{99m}$Tc injection is administered by intravenous injection. The dosage employed varies for each diagnostic procedure with due allowances being made for patient body weight. The suggested intravenous dose range employed in the average adult (70kg) for the various diagnostic procedures is as follows:

- Brain Scan: 370-740 MBq (10-20 mCi)
- Thyroid Gland Scan: 37-185 MBq (1-5 mCi)
- Salivary Gland Scan: 37-185 MBq (1-5 mCi)
- Blood Pool Imaging: 370-740 MBq (10-20 mCi)

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

Overdosage

In the event of an administration of a radiation overdose with Sodium pertechnetate $^{99m}$Tc, increasing the elimination of the radionuclide from the body should reduce the absorbed dose. Measures to reduce possible harmful effects include frequent voiding of urine and promotion of diuresis and faecal excretion. Very little treatment can be undertaken in the event of an overdose of $^{99m}$Tc labelled red blood cells since elimination is dependent on the normal haemolytic process.

Radiation Dosimetry

The estimated absorbed radiation doses to an average patient (70kg) from an intravenous injection of a maximum dose of 740 MBq of Sodium Pertechnetate $^{99m}$Tc administered with and without a thyroid blocking agent is shown in Table 6.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>With Blocking Agent</th>
<th>Without Blocking Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach Wall</td>
<td>2.4</td>
<td>21.5</td>
</tr>
<tr>
<td>Upper large Intestine</td>
<td>2.8</td>
<td>45.9</td>
</tr>
<tr>
<td>Lower large Intestine</td>
<td>3.3</td>
<td>16.3</td>
</tr>
<tr>
<td>Ovaries</td>
<td>3.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>3.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Testes</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.6</td>
<td>17.0</td>
</tr>
<tr>
<td>Bladder Wall</td>
<td>23.7</td>
<td>14.1</td>
</tr>
<tr>
<td>Effective Dose</td>
<td>3.5</td>
<td>8.9</td>
</tr>
</tbody>
</table>

Reference:

How Supplied

The generator is supplied in sizes ranging from 20 to 120 GBq and 370 GBq of $^{99}$Mo at 0900 hours Sydney time on the day of calibration.

The generator pack contains the following items for use in its elution:

(i) 1 Sterile generator.
(ii) 2 kits each containing 5x5mL or 5x10mL or 5x20mL vials of Sodium Chloride for Injections BP.
(iii) 2 kits each containing 5 x 30 evacuated vials, 5 sterile needles and 5 sterile mediswabs.
(iv) Elution vial shield with viewing window supplied with initial order only.

Expiry

The Sodium Pertechnetate $^{99m}$Tc Injection contains no bactericide and should not be used later than 8 hours after elution. The generator has an expiration time of 14 days after the date of calibration (shown on the generator label).

Storage

The generator is designed to operate at normal room temperature (below 30°C). The yield of Sodium Pertechnetate $^{99m}$Tc may be affected if the generator and the 0.9% sodium chloride solution are stored below room temperature.

Disposal of the Generator

The generator (and packaging) should be kept and not disposed of as normal waste within 70 days of the calibration date. Users are encouraged to return their generators to ANSTO Health for recycling. A special set of instructions and labels are included with each generator.

References

1. European Commision Committee for Proprietary Medicinal Products AD Hoc group on radiopharmaceuticals Technetium $^{99m}$Tc Generator Dec 1994 111/3143/93-En Final.

TGA Approved date: 24 January 1994
Amended: 23 June 2014

Contact Details:
ANSTO Health
Locked Bag 2001
Kirrawee DC NSW 2232
Telephone: 1800 251 572
Facsimile: 02 9543 6511

ANSTO Health is a commercial enterprise of the Australian Nuclear Science and Technology Organisation (ANSTO), which is located at Lucas Heights, in Sydney, NSW.

Product No: 10000
AUST R: 72820, 75859.
The generator is delivered in a kit that comes with Sodium Chloride BP injection vials, sterile swabs, needles and evacuated vials. The generators are sterile and pyrogen free when they leave ANSTO Health. Observe aseptic technique during the use of the generator.

First Elution
1. Remove generator and its accessories from the transport packaging. Install in the Gentech Garage or in the user shielding.
2. Lift Gentech handle. Rotate cover until you expose the yellow saline spike and outer filter. Push down handle to lock the lid in the operating position.
3. Remove flip off seal from saline vial (5, 10 or 20 mL). Recommended minimum elution volume is 5 mL. For elution volume between 5 and 20 mL, aseptically remove unwanted saline from 10 or 20 mL vials with hypodermic needle and discard.
4. Place Gentech 0.9% Sodium Chloride BP (Saline) vial into the New Gentech saline cover provided in the foam insert of the transport packaging with every generator. Swab the exposed part of the silicone septum with a preinjection swab provided. Allow to dry.
5. Remove the yellow protective cap from the Gentech saline spike.
6. Align the lugs of the Gentech saline cover with grooves in the port of the Gentech top and push down firmly. When vial is fully depressed, turn clockwise in direction of arrows to engage vial on the saline spike and lock the saline cover in place.
7. Remove white plastic lid from the elution vial shield. Unscrew metal top. Remove the red flip-off seal from the 30 mL evacuated elution vial. Place it on the elution vial shield and screw on the top to hold vial in place. Swab top of elution vial shield and the exposed part of the septum with a pre-injection swab provided. Allow to dry.
8. Grip the red protective cap (male luer closure), turn it anti-clockwise through 90° and remove from the outlet filter. With elution needle cover in place, attach a sterile elution needle (screw clockwise). (Caution: do not over-tighten). Remove elution needle cover.
9. With the evacuated vial now in place, invert elution vial shield over elution needle. Lower the elution vial shield until the evacuated vial is fully penetrated by the elution needle. Allow at least 3 minutes to complete elution.
10. Observe emptying of the saline vial and filling of the elution pot indicated by the sight and sound of air bubbles in the elution vial.
11. Check the saline vial is empty and through the elution vial shield window that the elution occurred. If elution did not occur, repeat steps 3 and 4 and 6 to 10 with a fresh evacuated vial.
12. Remove the elution vial shield from the elution needle. Cover elution vial shield with white plastic lid.
13. Put elution needle cover back on to the elution needle and leave it in place until next elution. (Replace with fresh sterile elution needle and cover before each elution).
14. Do not remove saline vial assembly until the next elution.
15. Affix label to the elution vial shield indicating elution time and date and that the contents are radioactive.
16. Assay the contents of the vial, for its $^{99mTc}$ contents using a previously calibrated $^{99mTc}$ dose calibrator (or other suitable measuring instrument). Record the results and calculate the total $^{99mTc}$ content of the vial.
17. Perform a gamma spectroscopy test to determine extent of molybdenum $[^{99}Mo]$ breakthrough. Alternate method described by Richards and O’Brien could also be used (Reference 3) page 3.

Subsequent Elutions
1. Remove used saline vial (by twisting anti-clockwise), then repeat steps 3, 4, and 6, 7.
2. Remove used elution needle (by twisting anti-clockwise) and replace with a fresh sterile elution needle.
3. Repeat steps 9 through to 17.

Troubleshooting Tips
When Generator is Not Eluting:
1. Check that the elution needle is not loose (see step 8).
2. Try another elution vial.
3. If you inadvertently remove the elution vial before it finishes eluting, the column will become wet and will need to be dried. Attach a fresh elution vial but do not replace the saline vial unless it still contains some saline. In this case replace with an empty saline vial - this will allow air (not saline) to pass through and this will make the column dry.
4. Call ANSTO Health on 1800 251 572.

To Prevent Damaging the Spike:
1. Ensure that the protective flip off seal is removed from the saline vial.
2. With every new generator ensure to use the new Gentech saline cover provided in the foam insert in the transport of every generator.
3. Ensure that the yellow protective cap is removed from the saline spike.
4. Ensure that the saline vial is placed on the spike vertically and not at an angle.