INSTITUTE OF NUCLEAR PHYSICS,
ACADEMY OF SCIENCE OF UZBEKISTAN

STATE ENTERPRISE «RADIOPREPARAT»

Generator of $^{99}$Mo/$^{99m}$Tc

TECHNICAL DESCRIPTION AND INSTRUCTIONS

TSH 42 -006-2008
Description and Composition of the Drug Product

**Name of the medicinal product:** Eluate of sodium pertechnetate-\(^{99m}\)Tc from radionuclide generator \(^{99}\)Mo/\(^{99m}\)Tc

**Pharmaceutical form:** Radiopharmaceuticals - solution for injection

**Description**
Radionuclide generator of \(^{99}\)Mo/\(^{99m}\)Tc produces sterile, endotoxin-free and isotonic water solution of sodium pertechnetate, Na\(^{99m}\)TcO\(_4\). This solution is eluted from the generator column filled with alumina on which Molybdenum-99 is adsorbed. Molybdenum -99 decays producing technetium-99m. The generator is supplied with the accessories which enable easy and safe operation of the generator. Sodium pertechnetate-\(^{99m}\)Tc can be used directly for diagnostics or for labelling of radiopharmaceuticals kits.

The sodium pertechnetate Na\(^{99m}\)TcO\(_4\) solution obtained from the generator meets the requirements of the European Pharmacopoeia (2002:0124).

**Composition of the medicinal product**
Eluate of sodium pertechnetate-\(^{99m}\)Tc from radionuclide generator \(^{99}\)Mo/\(^{99m}\)Tc contains:
- sodium pertechnetate, Na\(^{99m}\)TcO\(_4\)  \(0.5 - 15.0\) GBq/ml
- sodium chloride, NaCl  \(9\) mg/ml

<table>
<thead>
<tr>
<th>NAMES OF INGREDIENTS</th>
<th>UNIT AND/OR PERCENTAGE</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium Molybdate-(^{99})Mo</td>
<td>5.5 -18.5 GBq</td>
<td>precursor of drug substance</td>
</tr>
<tr>
<td>Sodium Pertechnetate-(^{99m})Tc</td>
<td>3.8 - 13.0 GBq</td>
<td>drug substance</td>
</tr>
<tr>
<td>Excipient(s):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>9 mg/ml</td>
<td>Isotonicity</td>
</tr>
<tr>
<td>Water for injection</td>
<td></td>
<td>Solvent</td>
</tr>
</tbody>
</table>

Calculation of the expected activity and elution yield should be performed according to the information delivered with the generator.

Radionuclidic generator of \(^{99}\)Mo/\(^{99m}\)Tc consists of:
- generator column (1) filled with alumina on which molybdenum-99 (enriched molybdenum-98) is adsorbed. The bottom end of the column is provided with a glass filter to prevent any leakage of alumina from the column. Top and bottom ends of the column are closed with rubber stoppers and caps;
- a set of stainless steel needles (2) which connects generator column with the eluent bottle and eluate vials;
- the column and the needles are placed inside lead shielding (3) of 35 or 50 mm wall thickness. This shielding protects personnel from radiation and allows easy operation of the generator. The thickness of the lead wall depends on the Molybdenum-99 activity adsorbed on the column;
- filter (4) of the eluate (0.45 \(\mu\)m pore size); air filter (9) - bacteriological filter (0.2 \(\mu\)m) to the vial with eluant
- two vials containing bacteriostatic agent (0.02% water solution of lauryldimethylbenzylammonium bromide) which protect the generator needles during transportation and during brakes between elutions;
- eluate volume controller (5). Construction of this device enables obtaining of the required eluate volume (by changing the volume of the eluent from 4 to 8 ml). The accuracy of the volume
control is within 0.5 ml. This helps to obtain the required radioactive concentration of $^{99m}$Tc in the solution. The regulation of the eluate volume is made by turning the bushing (7) of the controller so, that the pointer (6) matches the number of eluate milliliters on the upper surface of the bushing.

The construction of the generator is presented in the Figure 1 below.

![Figure 1: Schematic view of the generator $^{99}$Mo/$^{99m}$Tc](image)

**Technical parameters:**
- Weight of generator: 12 or 16 kg
- Dimensions of the generator: 133 x 160 x 290 mm.

**Immediate packaging**
- For active ingredient – sodium molybdate - $^{99}$Mo
  - The generator contains fission produced molybdenum-99 adsorbed on alumina in sterilized glass column surrounded by lead shielding.
- For eluent and for eluate
  - The type I glass container – according to Eu. Pharmacopoeia 4-th edition, chapter 3.2.1.
  - The borosilicate glass vial, neutral, of 10 ml volume. They are closed with grey rubber stoppers type I according to Eu. Pharmacopoeia 4-th edition, chapter 3.2.9. and aluminum cap.

**Procedures for waste and waste disposal**
- After expiry each generator is treated as waste and should be handled according to the regulations of the country, where it was exploited. The eluate of sodium pertechnetate-$^{99m}$Tc which was not used can be cooled down and treated as low activity waste. Technetium-99m decays with the half-life of 6.02 hours to technetium-99 which is considered quasi stable.

**Pharmaceutical Development**
Components of the Drug Product

Drug Substance

Eluate of sodium pertechnetate-\(^{99m}\)Tc is delivered from sterile \(^{99}\)Mo/\(^{99m}\)Tc generator which is a convenient source of pertechnetate in sterile, endotoxin free, isotonic solution ready for intermediate oral or intravenous administration or for aseptic preparation of technetium-99m labeled radiopharmaceuticals. Molybdenum-99 (T\(_{1/2} = 66\) h) decays producing technetium-99m, a monoenergetic gamma emitter (T\(_{1/2} = 6.02\) h, E\(_\gamma = 140.5\) keV), with associated 0.0005\% beta emission. \(^{99m}\)Tc decays by isomeric transition to technetium-99 which is considered quasi stable. Correction factors for calculation of molybdenum decay and technetium-99m in growth in the time between elutions are presented below:

<table>
<thead>
<tr>
<th>Time elapsed since the last elution was performed (h)</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correction factor for decay of (^{99})Mo</td>
<td>1.0</td>
<td>0.979</td>
<td>0.960</td>
<td>0.940</td>
<td>0.919</td>
<td>0.900</td>
<td>0.881</td>
<td>0.863</td>
<td>0.845</td>
<td>0.828</td>
<td>0.811</td>
<td>0.785</td>
</tr>
<tr>
<td>(^{99m})Tc growth factor</td>
<td>0.0</td>
<td>0.21</td>
<td>0.39</td>
<td>0.51</td>
<td>0.62</td>
<td>0.71</td>
<td>0.79</td>
<td>0.85</td>
<td>0.89</td>
<td>0.93</td>
<td>0.96</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Excipients

Sodium chloride, NaCl
Sodium chloride present in the eluate from radionuclide generator assures its isotonicity.

Water for injection
Water acts a solvent role

Drug Product

Formulation Development
Not applicable

Overages
Not applicable

Physicochemical and Biological Properties
characteristics of the sodium pertechnetate \(^{99m}\)Tc solution to be used:
- pH: 5.5 – 7.5
- sterile
- bacterial endotoxins in international endotoxin units per dose injected: < 0.125 EU/ml
- contents of aluminum: < 5\(\mu\)g/ml
- radiochemical purity: > 99\%
- radionuclide purity at the calibration date in %
  \(^{99}\)Mo: < 0.02

Manufacturing Process Development
Not applicable
**Container Closure System**

The generator column containing alumina on which $^{99}$Mo is absorbed and located inside lead shielding. Then it is packed in a plastic container and closed with a lid (immediate package). This plastic container together with kit for elution (8 vacuum vials and 8 vials with eluent), instruction of use and certificate of the radioactive source is placed in a different transport packages in dependence from the radioactiv

**Microbiological Attributes**

Eluate of sodium pertechnetate-$^{99m}$Tc is provided by sterile $^{99}$Mo/$^{99m}$Tc generator which is a convenient source of pertechnetate in sterile, free from bacterial endotoxines, isotonic solution. The generator contains fission produced molybdenum-99 adsorbed on alumina in sterilized glass column surrounded by lead shielding. Bacteriological filter is installed additionally assuring sterility of the eluate. The column may be eluted aseptically using sterile evacuated elution vials and eluent consisting of saline isotonic solution. The generator is supported with two vials containing bacterioststic agent (0.2% water solution of lauryldimethylbenzylammonium bromide, CAS# [7281-04-1]) which protect sterile generator needles in transportation and during brakes between elutions.

**Compatibility**

Not applicable

**CLINICAL PHARMACOLOGY**

The pertechnetate ion distributes in the body similarly to the iodide ion but is not organified when trapped in the thyroid gland. Pertechnetate tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. It also concentrates in the thyroid gland, salivary glands, stomach and choroid plexus. After intravenous administration it remains in the circulatory system for sufficient time to permit blood pool, organ perfusion, and major vessel studies. It gradually equilibrates with the extracellular space. A fraction is promptly excreted via the kidneys.

Following the administration of Sodium Pertechnetate Tc-99m as an eye drop, the drug mixes with tears within the conjunctival space. Within seconds to minutes it leaves the conjunctival space and escapes into the inferior meatus of the nose through the nasolacrimal drainage system. During this process the pertechnetate ion passes through the canaliculi, the lacrimal sac and the nasolacrimal duct. In the event of any anatomical or functional blockage of the drainage system there will be a backflow resulting in tearing (epiphora). Thus the pertechnetate escapes the conjunctival space in the tears.

While the major part of the pertechnetate escapes within a few minutes of normal drainage and tearing, it has been documented that there is some degree of transconjunctival absorption with turnover of 1.5% per minute in normal individuals, 2.1% per minute in patients without any sac and 2.7% per minute in patients with inflamed conjunctiva due to chronic dacryocystitis. Individual values may vary but these rates are probably representative and indicate that the maximum possible pertechnetate absorbed will remain below one thousandth of that used in other routine diagnostic procedures.

**INDICATIONS AND USAGE**

Sodium Pertechnetate Tc-99m is used IN ADULTS as an agent for:
- Brain Imaging (including cerebral radionuclide angiography)
- Thyroid Imaging
- Salivary Gland Imaging
- Placenta Localization
Blood Pool Imaging (including radionuclide angiography)
Urinary Bladder Imaging (direct isotopic cystography) for detection of vesico-ureteral reflux
Nasolacrimal Drainage System Imaging (dacryoscintigraphy)
Sodium Pertechnetate Tc-99m is used IN PEDIATRIC PATIENTS as an agent for:
  Brain Imaging (including cerebral radionuclide angiography)
  Thyroid Imaging
  Blood Pool Imaging (including radionuclide angiography)
  Urinary Bladder Imaging (direct isotopic cystography) for the detection of vesico-ureteral reflux

**CONTRAINdications**
None known.

**WARNINGS**
Radiation risks associated with the use of Sodium Pertechnetate Tc-99m are greater in pediatric patients than in adults and, in general, the younger the patient the greater the risk owing to greater absorbed radiation doses and longer life expectancy. These greater risks should be taken firmly into account in all benefit risk assessments involving pediatric patients.

**PRECAUTIONS**
As in the use of any radioactive material, care should be taken to minimize radiation exposure to the patient consistent with proper patient management and to insure minimum radiation exposure to occupational workers.
Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. After the termination of the nasolacrimal imaging procedure, blowing the nose and washing the eyes with sterile distilled water or an isotonic sodium chloride solution will further minimize the radiation dose.
Since the eluate does not contain an antimicrobial agent, it should not be used after 12 hours from time of generator elution.
Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether Sodium Pertechnetate Tc-99m may affect fertility in males or females.
Pregnancy Category C
Animal reproductive studies have not been conducted with Sodium Pertechnetate Tc-99m. It is also not known whether Sodium Pertechnetate Tc-99m can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Sodium Pertechnetate Tc-99m should be given to pregnant women only if the expected benefits to be gained clearly outweigh the potential hazards. Ideally, examinations using radiopharmaceutical drug products - especially those elective in nature - of women of childbearing capability should be performed during the first ten days following the onset of menses.
Nursing Mothers
Technetium Tc-99m is excreted in human milk during lactation, therefore, formula-feedings should be substituted for breast-feedings.

**Pediatric Use**
See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections. Also see the description of additional risk under WARNINGS.

**ADVERSE REACTIONS**
Allergic reactions including anaphylaxis have been reported infrequently following the administration of Sodium Pertechnetate Tc-99m.
DOSAGE AND ADMINISTRATION

Sodium Pertechnetate Tc-99m is usually administered by intravenous injection, but can be given orally. When imaging the nasolacrimal drainage system, instill the Sodium Pertechnetate Tc-99m by the use of a device such as a micropipette or similar method which will ensure the accuracy of the dose.

For imaging the urinary bladder and ureters (direct isotopic cystography), the Sodium Pertechnetate Tc-99m is administered by direct instillation aseptically into the bladder via a urethral catheter, following which the catheter is flushed with approximately 200 mL of sterile saline directly into the bladder.

The dosage employed varies with each diagnostic procedure. If the oral route is elected, the patient should fast for at least six (6) hours before and two (2) hours after administration.

The suggested dose ranges employed for various diagnostic indications in the average ADULT PATIENT (70 kg) are as follows:

- Vesico-ureteral imaging: 18.5 to 37 MBq (0.5 to 1 mCi)
- Brain imaging: 370 to 740 MBq (10 to 20 mCi)
- Thyroid gland imaging: 37 to 370 MBq (1 to 10 mCi)
- Salivary gland imaging: 37 to 185 MBq (1 to 5 mCi)
- Placenta localization: 37 to 111 MBq (1 to 3 mCi)
- Blood pool imaging: 370 to 1110 MBq (10 to 30 mCi)
- Nasolacrimal drainage system: Maximum dose of 3.7 MBq (100 μCi)

The recommended dosages in PEDIATRIC PATIENTS are:

- Vesico-ureteral imaging: 18.5 to 37 MBq (0.5 to 1 mCi)
- Brain imaging: 5.18 to 10.36 MBq (140 to 280 μCi) per kg body weight
- Thyroid gland imaging: 2.22 to 2.96 MBq (60 to 80 μCi) per kg body weight
- Blood pool imaging: 5.18 to 10.36 MBq (140 to 280 μCi) per kg body weight

Minimum dose of 111 to 185 MBq (3 to 5 mCi) should be employed if radionuclide angiography is performed as part of the brain imaging or blood pool imaging procedures.
<table>
<thead>
<tr>
<th>Days</th>
<th>Activity of $^{99}$Mo, MBq</th>
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<tbody>
<tr>
<td></td>
<td>18500</td>
</tr>
<tr>
<td>1</td>
<td>12900</td>
</tr>
<tr>
<td>2</td>
<td>10000</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>13</td>
<td>630</td>
</tr>
<tr>
<td>14</td>
<td>500</td>
</tr>
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<table>
<thead>
<tr>
<th>Activity of $^{99m}$Tc, MBq</th>
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</thead>
<tbody>
<tr>
<td>11100</td>
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