BRAIN-SPECT kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

I vial contains:

Active substance: Examinetate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

It is a radiopharmaceutical kit for preparation of 99mTc-Exametazime. BRAIN-SPECT kit contains:

The pharmaceutical form of BRAIN-SPECT kit is powder for injection according to the determination of Ph. Eur.

The kit contains a lyophilized, sterile, pyrogen free inactive preparation sealed in nitrogen atmosphere, ready for one-step labeling with oxidizing agent free sodium pertechnetate sterile injection (Ph.Eur.). The product is to be used for isotope diagnostic study.

4. CLINICAL PARTICULARS

4.1 Diagnostic indications

This medical product is for diagnostic use only.

After labeling with sodium pertechnetate (99mTc) sterile solution, it is for the following diagnostic study:

– Regional cerebral blood flow (stoke, carotid artery occlusion, transient ischemic attack, migraine, tumors of the brain, dementia differential diagnosis),
– BRAIN-SPECT kit can be applied for detection, localization of cortical areas with decreased perfusion, and to estimate the extent of the damage.
– Detection of affected cortical area in 1-2 cm is feasible by planar gamma camera, the smaller areas can be detected by SPECT.

4.2 Posology and method of administration

Posology: The reconstituted kit with 370 - 2200 MBq of sterile oxidant-free Tc-99m Sodium Pertechnetate solution in 5 ml. Depending on the activity, one vial of Tc-99m-HM-PAO can be divided into two parts for SPECT, and into three parts for planar imaging.

Method of Administration: Intravenously. Brain imaging may begin 2 minutes after intravenous injection. 

The is 370-740 MBq (10-20 mCi) by intravenous injection.

Recommended Activity:

<table>
<thead>
<tr>
<th>Adult dose</th>
<th>370-740 MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>F = (A+1)/(A+7)</td>
</tr>
<tr>
<td>kg</td>
<td>mBq</td>
</tr>
<tr>
<td>3 kg</td>
<td>9.03</td>
</tr>
<tr>
<td>4 kg</td>
<td>15.52</td>
</tr>
<tr>
<td>5 kg</td>
<td>19.69</td>
</tr>
<tr>
<td>6 kg</td>
<td>22.22</td>
</tr>
<tr>
<td>7 kg</td>
<td>24.24</td>
</tr>
<tr>
<td>8 kg</td>
<td>26.00</td>
</tr>
<tr>
<td>9 kg</td>
<td>27.56</td>
</tr>
<tr>
<td>10 kg</td>
<td>28.86</td>
</tr>
</tbody>
</table>

4.3 Contraindications

Contraindications are not known in case of BRAIN-SPECT.

4.4 Special warnings and precautions for use

Only qualified person may only be used radiopharmaceuticals with the appropriate government authorities for use in the preparation of radiopharmaceuticals. Contents of the vial are intended only for use in the preparation of 99mTc-BRAIN-SPECT and are not to be administered directly to the patient without first undergoing the labeling procedure. Use only from the flask of oxidizing agent stored at 2-8 °C. Use the vial of sterile oxidant-free 99mTc sodium pertechnetate for up to 24 hours. Use only vials taken from the generator less than 2 hours before reconstitution.

Radioactive drugs must be handled with care and appropriate safety measures should be taken to minimize radiation exposure to clinical personnel.

Contents of the kit before preparation are not radioactive, after addition of Sodium Pertechnetate (99mTc) sterile injection adequate shielding of the final preparation.

The components of the kit are sterile and non-pyrogenic, therefore it is essential to follow the guide of strict aseptic procedure.

Patient are advised drink plenty of fluids following the scan to improve excretion and minimizing the absorbed dose.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions have not been known up to now.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

The labelled product should be used within 1 hours after reconstitution with sodium 99mTc-pertechnetate sterile injection containing oxidizing agent.

5.2 Pharmacokinetic properties

Technetium (99mTc) exametazime is a lipophilic complex able to cross the blood-brain barrier as well as penetrate cell membranes. The agent localizes in the brain as a function of regional cerebral perfusion.

Effective dose equivalent delivered from radiation dose of most diagnostic investigation is less than 20 mWV.

5.4 Overdose

No case of overdose has been reported. In the event of the administration of a radiation overdose frequent monitoring and correction should be encouraged in order to minimize the absorbed dose to patient.

6. ADVERSE REACTIONS

6.1 List of adverse reactions

These adverse effects will occur with low frequency because of the low radiation doses incurred. The effective dose equivalent delivered from radiation dose of most diagnostic investigation is less than 20 mWv.

7. PHARMACOLOGICAL PARTICULARS

6.2 Incompatibilities

The labelling procedure using 99mTc-sodium pertechnetate sterile injection (Ph.Eur.) depends on the amount of the tin level in reduced form. Therefore it is not allowed to use 99mTc-sodium pertechnetate sterile injection containing oxidizing agent.

7. SHELF LIFE

Before reconstitution BRAIN-SPECT has to be stored at 2-8 °C protected from light. After reconstitution BRAIN-SPECT has to be stored below 25 °C protected from light. The labelled product should be used within 1 hours after reconstitution with sodium 99mTc-pertechnetate injection.

The expiry date for the kit is 1 year.

6.3 Special precautions for storage

The kit should be stored at 2-8 °C. Storage of labeled product should be in accordance with national regulations for radiomaterials.

The contents of the vials are intended only for use in the preparation of radiopharmaceuticals 99mTc-technetium labelled injection, using the procedure described in package information booklet.

6.4 Nature and contents of container

Sterile, 8 ml colourless, European Pharmacopoeia Type 1, borosilicate glass vials, closed with sterile rubber stopper and plastic-aluminium cups with turned up edge.

7. MARKETING AUTHORISATION HOLDER

Name: MEDI-RADIOPHARMA LTD.
Address: 2030, Érd Szamos st. 10-12. Hungary
Telephone: +36-23-521-261
Fax: +36-23-521-260
e-mail: medi-radiopharma-ltd@medi-radiopharma.hu

8. MARKETING AUTHORIZATION NUMBER(S)

(Hungary) OGYI-T-673531/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

Date of last renewal: 17 December, 2008.


11. DOSIMETRY

Technetium (99mTc) degrades with the emission of gamma radiation with energy of 140 keV and a half-life of 6 hours to technetium-99 which can be regarded as quasi-stable.

Adult and Children Category

Estimated Absorbed Radiation Dose after administration of Technetium (99mTc) BRAIN-SPECT Injection

Absorbed radiation dose

<table>
<thead>
<tr>
<th>Target organ</th>
<th>Adult mgY/mGy</th>
<th>15 years mgY/mGy</th>
<th>10 years mgY/mGy</th>
<th>5 years mgY/mGy</th>
<th>newborn mgY/mGy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenals</td>
<td>5.12E+03</td>
<td>6.56E+03</td>
<td>9.84E+03</td>
<td>1.42E+02</td>
<td>2.32E+02</td>
</tr>
<tr>
<td>Brain</td>
<td>3.12E+03</td>
<td>3.12E+02</td>
<td>3.12E+02</td>
<td>2.33E+02</td>
<td>9.32E+02</td>
</tr>
<tr>
<td>Breast</td>
<td>1.04E+03</td>
<td>1.23E+03</td>
<td>2.93E+03</td>
<td>3.57E+03</td>
<td>3.60E+03</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.10E+02</td>
<td>2.42E+02</td>
<td>3.22E+02</td>
<td>5.49E+02</td>
<td>1.54E+01</td>
</tr>
<tr>
<td>LLI Wall</td>
<td>2.18E+02</td>
<td>2.30E+02</td>
<td>4.63E+02</td>
<td>7.45E+02</td>
<td>1.46E+01</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>2.66E+02</td>
<td>2.68E+02</td>
<td>4.64E+02</td>
<td>8.56E+02</td>
<td>1.58E+01</td>
</tr>
<tr>
<td>Stomach</td>
<td>4.96E+02</td>
<td>5.34E+02</td>
<td>5.46E+02</td>
<td>5.18E+02</td>
<td>2.73E+02</td>
</tr>
</tbody>
</table>
12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The technetium (99mTc) labelling reaction involved in preparing technetium (99mTc) exametazime injection depends on maintaining tin in the divalent (reduced) state. Any oxidant present in the sodium pertechnetate (99mTcO4-) employed may adversely affect the quality of the preparation. Sodium pertechnetate (99mTcO4-) containing oxidants should not be used for the preparation of the labelled product.

To meet the last requirement, a generator must be eluted within 24 hours prior to any eluate for reconstitution with the BRAIN-SPECT kit.

Sodium Chloride Injection, (Ph.Eur.) must be used as the diluent. Do not use bacteriostatic sodium chloride as a diluent for sodium pertechnetate (99mTcO4-) injection because it will increase the oxidation products and adversely affect the biological distribution of BRAIN-SPECT.

The contents of the BRAIN-SPECT vial are sterile and pyrogen free. The vial contains no bacteriostatic preservatives. It is essential that the user follow the directions carefully and adhere to strict aseptic procedures during preparation of the radiopharmaceutical.

Radiochemical purity determination must be performed before administration to the patient. Three potential radiochemical impurities may be present in the prepared injection of the lipophilic technetium (99mTc) complex.

1. Place the vial containing the labelled substance in a lead shield.
2. Inject sterile sodium pertechnetate (99mTcO4-) solution (370-2200 MBq) aseptically into the vial containing a volume of 5 ml. Before removing the syringe, withdraw an equal volume of the nitrogen gas to normalise the pressure in the vial. (Do not use a breather needle.)
3. Dissolve the labelled material by gently swirling, incubate at room temperature for 5 min., and then shake gently before injection. (Adjust the volume if necessary with oxidant-free physiological saline and vial of chloroform.)
4. After reconstitution, store the labelled BRAIN-SPECT below 25°C protected from light.
5. The labelled preparation is to be used within 1 hour. Within this period the total amount of 99mTc-HMPAO complex should not be less than 80%.

Method I

Quality control
The quality of labelling (radiochemical purity) can be checked according to the organic solvent extraction method. The percentage of Lipophilic 99mTc-BRAIN-SPECT can be determined by this method.

Materials and equipments
- Saline
- Chloroform
- Vortex Mixer
- Dose calibrator

Procedure
1. Add 0.1 ml of the labelled compound into a vial, which contains 3 ml of chloroform and 2.9 ml of saline.
2. Close the vial, mix on a vortex mixer for 1 min. and thereafter wait for separation of phases (12-15 min).
3. Transfer the top layer (saline) to another vial and measure the activities of both phases (vial of saline and vial of chloroform) in a dose calibrator separately. The lipophilic 99mTc-HMPAO is in the chloroform fraction and the contaminants are in the saline layer.
4. Calculate the percentage of 99mTc-BRAIN-SPECT (radiochemical purity):

\[
\text{Percentage of radiochemical purity} = \frac{A_{\text{chloroform}}}{A_{\text{saline}} + A_{\text{chloroform}}} \times 100
\]

The percentage of radiochemical purity should not be less than 80% within 1 hour.

Method II

Quality control
Radiochemical purity according to 6Ph.Eur. Three potential radiochemical impurities may be present in the prepared exametazime injection. These are a secondary technetium (99mTc) exametazime complex, free pertechnetate and reduced-hydrolysed-technetium (99mTc). A combination of two chromatographic systems is necessary for the determination of the radiochemical purity of the injection.

Materials and equipments
- 0.9% sodium chloride
- 0.9% methyl Alcohol (MEK)
- 3% Toluene gel plate R, use a glass-fibre plate (2cm x 2cm)
- 3 x 4 inch TLC plates
- 4 x 4 cm TLC plates
- 4 tanks
- suitable counting equipment

Interpretation of Chromatogram
System 1 (TLC MEK)
- Secondary technetium (99mTc) exametazime complex and reduced-hydrolysed-technetium remain at the origin.
- Lipophilic technetium (99mTc) exametazime complex and pertechnetate migrate at Rf 0.8-1.0.

System 2 (TLC: 0.9% sodium chloride)
- Lipophilic technetium (99mTc) exametazime complex, secondary technetium (99mTc) exametazime complex and reduced-hydrolysed-technetium remain at the origin.
- Pertechnetate migrates at Rf 0.8-1.0.

Procedure
1. Prepare 2 chromatographic tanks containing one of them, fresh MEK and the other 0.9% sodium chloride.
2. Prepare TLC silica gel plate R, use a glass-fibre plate. Each is marked by the manufacturer 3.0 cm from the bottom as the point of origin.
3. Reconstitute a Brain-Spect vial according to this insert.
4. Apply at least 5 x samples of Brain-Spect approximately 2 cm from the bottom of two TLC silica gel plate R, use a glass-fibre plate strips (2cm x 2cm).
5. The strips are then immediately placed in prepared ascending chromatography development tanks, one containing MEK and the other 0.9% NaCl (1cm depth fresh solvent).
6. After a 15 cm elution the strips are removed, solvent fronts marked, the strips dried and the distribution of activity determined using suitable equipment.
7. Calculate the percentage of activity due to both secondary technetium (99mTc) exametazime complex and reduced-hydrolysed-technetium (99mTc) from System 1 (A%). Calculate the percentage of activity due to pertechnetate from System 2 (%B).
8. The radiopurity (as percentage lipophilic technetium (99mTc) exametazime complex) is given by:

\[
\text{Radiopurity} = \frac{A_{\text{MEK}}}{A_{\text{MEK}} + A_{\text{Sodium chloride}}} \times 100
\]

A% represents the level of secondary technetium (99mTc) exametazime complex plus reduced-hydrolysed-technetium (99mTc).
B% represents the level of pertechnetate.

The radiopurity of a lipophilic 99mTc of at least 80% may be expected provided the test samples have been taken and analysed within 60 minutes of reconstitution.