1. NAME OF THE MEDICINAL PRODUCT

BRAIN-SPECT kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
Active substance:
Exametazime 0.30 mg
Excipient(s):
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

It is a radiopharmaceutical kit for preparation of ^{99m}Tc-Exametazime.
BRAIN-SPECT kit contains:
The pharmaceutical form of BRAIN-SPECT kit is powder for injection according 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 medicinal product is for diagnostic use only.
After labelling with sodium pertechnetate (^{99m}Tc) sterile solution, it is for the following diagnostic study:
- Regional cerebral blood flow (stroke, carotid artery occlusion, transient ischaemic attack, migraine, tumours of the brain, dementia differential diagnosis,
- BRAIN-SPECT kit can be applied for detection, localisation of cortical areas with decreased perfusion, and to estimate the extent of the damage.
- Detection of affected cortical areas over 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 vial is reconstituted 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:

Adult dose: 370-740 MBq
Children: F (A+1)/(A+7)

F = factor according to the table below
A = age

3 kg = 0.10	12 kg = 0.32	22 kg = 0.50	32 kg = 0.62	42 kg = 0.78	52-54 kg = 0.90
4 kg = 0.14	14 kg = 0.36	24 kg = 0.53	34 kg = 0.64	44 kg = 0.80	56-58 kg = 0.92
6 kg = 0.19	16 kg = 0.40	26 kg = 0.56	36 kg = 0.66	46 kg = 0.82	60-62 kg = 0.96
8 kg = 0.23	18 kg = 0.44	28 kg = 0.58	38 kg = 0.68	48 kg = 0.85	64-66 kg = 0.98
10 kg = 0.27	20 kg = 0.46	30 kg = 0.60	40 kg = 0.70	50 kg = 0.88	68 kg = 0.99

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 radiopharmaceutical agents with the appropriate government authorisation for use and manipulation of radionuclides.
Contents of the vial are intended only for use in the preparation of ^{99m}Tc BRAIN-SPECT and are not to be administered directly to the patient without first undergoing the labelling procedure.
Use only eluate from a ^{99m}Tc generator previously eluted within 24 hours. Use only eluate taken from 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 (^{99m}Tc) sterile injection adequate shielding of the final preparation must be maintained.
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 extcretion 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 know.

4.6 Pregnancy and lactation

Women of childbearing potential
When it is necessary to inject radiopharmaceuticals to women of childbearing potential, information should always be thought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainly exists it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques, which do not involve ionising radiation should always considered.
Pregnancy
Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only imperative investigations should-therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.
Lactation
Before administering radiopharmaceuticals to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until after the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceuticals has been made, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted for 12 hours and the expressed feeds discarded. Breast feeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1mSv.

4.7 Effects on ability to drive and use machines

BRAIN-SPECT has no effect on the ability to drive or operate machines.

4.8 Undesirable effects

A very few cases of mild hypersensitivity evidenced by the development of an urticarial erythematous rash have been reported following direct intravenous injection of the reconstituted product. A very few reports have also been received of hypersensitivity reactions, possibly anaphylactic in nature, following administration of technetium-99m- labelled leucocytes prepared using Technetium [^{99m}Tc]-exametazime.
For each patient, exposure to ionising radiation must be justified on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic result.
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that 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 mSv.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

ATC code: V09BA01
At the chemical concentrations and activities used for diagnostic procedures technetium [^{99m}Tc]-exametazime does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

Technetium (^{99m}Tc) 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. Its radionuclide emissions while localized in cerebral tissue permit external imaging of the cerebral distribution of the agent thus helping detect altered regional cerebral perfusion. Technetium (^{99m}Tc) exametazime is primarily extracted and trapped by cerebral gray matter and the basal ganglia during the first pass through the brain. It has been proposed that the retention in the brain of ^{99m}Tc exametazime results from in vivo conversion of the primary complex to a less lipophilic complex, which is unable to cross the blood-brain barrier.
Uptake in the brain reaches a maximum of 3.5-7.0% of the injected dose between 30-60 sec after injection. Up to 15% of the cerebral activity washes out of the brain 2 minutes post injection after which there is little loss of activity for the following 24 hours except by physical decay of technetium-99m. The activity not associated with the brain is widely distributed throughout the body particularly in muscle and soft tissue. About 20% of the injected dose is removed by the liver immediately after injection and excreted through the hepatobiliary system. About 40% of the injected dose is excreted through the kidneys and urine over the 48 hours after injection resulting in a reduction in general muscle and soft tissue background.

5.3 Preclinical safety data

Non-clinical data show no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
Pathological investigations during preclinical studies did not reveal pathological lesions in the organs of the laboratory animals. Mutagenicity, teratogenicity or carcinogenicity of the product has not been reported in the relevant literature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous (II) Chloride Dihydrate	3,8 µg
Tetrasodium Pyrophosphate Decahydrate	2,52 mg

6.2 Incompatibilities

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

6.3 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 ^{99m}Tc-pertechnetate injections.
The expiry date for the kit is 1 year.

6.4 Special precautions for storage

The kit should be stored at 2-8 °C.
Storage of labelled product should be in accordance with national regulations for radioactive materials.
The contents of the vial are intended only for use in the preparation of radioactive ^{99m}Tc-technetium labelled injection, using the procedure described in package information leaflet.
Radiopharmaceutical 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 licence the use of radionuclides.

6.5 Nature and contents of container

Sterile, 8 ml, colourless, European Pharmacopoeia Type I, borosilicat glass vials, closed with sterile rubber stopper and plastic-aluminium caps with turned up edge.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements for radioactive materials.

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
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8. MARKETING AUTHORISATION NUMBER(S)

Hungary: OGYI-T-8733/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Hungary:
Date of first authorisation: 23. January, 1991
Date of last renewal of the authorisation: 17. December, 2008.

10. DATE OF REVISION OF THE TEXT

19. March, 2021

11. DOSIMETRY

Technetium (^{99m}Tc) disintegrates 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 (^{99m}Tc) BRAIN-SPECT Injection

Absorbed radiation dose

Target organ	Adult mGy/MBq	15 years mGy/MBq	10 years mGy/MBq	5 years mGy/MBq	1 year mGy/MBq	newborn mGy/MBq
Adrenals	5.12E-03	6.56E-03	9.84E-03	1.42E-02	2.32E-02	4.48E-02
Brain	7.51E-03	1.21E-02	1.76E-02	2.30E-02	4.06E-02	9.32E-02
Breast	1.04E-03	1.23E-03	2.29E-03	3.57E-03	6.05E-03	1.24E-02
Gallbladder Wall	2.10E-02	2.42E-02	3.22E-02	5.49E-02	1.54E-01	3.19E-01
LLI Wall	2.18E-02	2.80E-02	4.63E-02	7.45E-02	1.40E-01	3.41E-01
ULI Wall	2.60E-02	2.68E-02	4.46E-02	8.56E-02	1.58E-01	3.64E-01
Small Intestine	2.11E-02	6.48E-03	7.38E-03	7.07E-02	1.31E-01	3.09E-01
Stomach	4.90E-03	3.34E-02	5.46E-02	1.58E-02	2.73E-02	6.42E-02
Heart Wall	2.64E-03	3.50E-03	5.10E-03	7.58E-03	1.26E-02	2.43E-02
Kidneys	3.77E-02	4.51E-02	6.29E-02	9.01E-02	1.56E-01	3.86E-01
Liver	1.75E-02	2.25E-02	3.33E-02	4.71E-02	8.42E-02	1.79E-01
Lung	1.08E-02	1.58E-02	2.20E-02	3.35E-02	6.36E-02	1.65E-01
Muscle	1.84E-03	2.35E-01	3.44E-03	5.27E-03	9.50E-03	1.95E-02
Ovaries	1.33E-02	1.45E-02	3.00E-02	4.85E-02	9.99E-02	2.06E-01
Pancreas	4.90E-03	6.34E-03	9.63E-03	1.50E-02	2.44E-02	4.75E-02
Red Marrow	2.63E-03	3.25E-03	4.54E-03	6.10E-03	1.02E-02	1.90E-02
Bone Surfaces	3.13E-03	4.26E-03	6.55E-03	1.04E-02	1.90E-02	3.76E-02
Skin	7.10E-04	9.03E-04	1.47E-03	2.41E-03	4.90E-03	1.11E-02
Spleen	3.03E-03	4.27E-03	6.53E-03	1.01E-02	1.66E-02	3.19E-02
Testes	1.81E-03	3.70E-03	2.19E-02	2.62E-02	3.67E-02	5.59E-02
Thymus	1.10E-03	1.43E-03	2.09E-03	3.17E-03	5.08E-03	1.01E-02
Thyroid	5.11E-04	7.83E-04	1.38E-03	2.24E-03	4.16E-03	8.75E-03
Urinary Bladder Wall	1.06E-02	1.35E-02	2.00E-02	3.04E-02	5.44E-02	1.26E-01
Uterus	5.93E-03	7.47E-03	1.19E-02	1.79E-02	2.94E-02	5.56E-02
Total Body	3.01E-03	3.94E-03	6.24E-03	1.00E-02	1.89E-02	4.20E-02
EDE (mSv/MBq)	**1.18E-02**	**1.56E-02**	**2.58E-02**	**4.04E-02**	**7.97E-02**	**1.80E-01**

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No.1 Society of Nuclear Medicine, 1976). Effective dose equivalents (EDE) were calculated in accordance with ICRP 53 (Ann. ICRP 18 (1-4), 1988) and gave values of 1.18 x 10^{-2} mSv/MBq for adults, 1.56 x 10^{-2} mSv/MBq, 2.58 x 10^{-2} mSv/MBq, 4.04 x 10^{-2} mSv/MBq, 7.97 x 10^{-2} mSv/MBq and 18.0 x 10^{-2} mSv/MBq for children 15 year, 10 year, 5 year, 1 year and for newborn, respectively.

Pregnancy Category

Estimated Absorbed Radiation Dose after administration of Technetium Tc99m BRAIN-SPECT Injection

	Absorbed radiation dose			
Target organ	Female mGy/MBq	3 month mGy/MBq	6 month mGy/MBq	9 month mGy/MBq
Adrenals	6.57E-03	6.57E-03	6.58E-03	8.04E-03
Brain	1.35E-02	1.35E-02	1.35E-02	1.35E-02
Breast	1.22E-03	1.23E-03	1.42E-03	1.59E-03
Gallbladder Wall	2.43E-02	2.45E-02	2.36E-02	2.99E-02
LLI Wall	2.46E-02	2.46E-02	2.18E-02	2.01E-02
ULI Wall	3.08E-02	3.10E-02	2.38E-02	2.09E-02
Small Intestine	2.61E-02	2.58E-02	2.32E-02	2.55E-02
Stomach	6.26E-03	6.39E-03	6.19E-03	9.07E-03
Heart Wall	3.50E-03	3.51E-03	3.49E-03	4.02E-03
Kidneys	4.13E-02	4.13E-02	4.11E-02	4.20E-02
Liver	2.24E-02	2.25E-02	2.24E-02	2.39E-02
Lung	1.39E-02	1.39E-02	1.39E-02	1.42E-02
Muscle	2.33E-03	2.21E-03	2.14E-03	1.91E-03
Ovaries	1.42E-02	1.33E-02	8.86E-03	6.68E-03
Pancreas	6.34E-03	6.37E-03	6.40E-03	1.20E-02
Red Marrow	3.30E-03	3.25E-03	2.72E-03	2.50E-03
Bone Surfaces	4.33E-03	4.30E-03	3.94E-03	3.89E-03
Skin	9.10E-04	9.15E-04	8.74E-04	8.85E-04
Spleen	4.28E-03	4.30E-03	4.18E-03	5.69E-03
Testes	1.41E-03	1.41E-03	1.42E-03	1.54E-03
Thymus	1.41E-03	1.41E-03	1.42E-03	1.54E-03
Thyroid	5.40E-04	5.40E-04	5.71E-04	5.89E-04
Urinary Bladder Wall	1.51E-02	1.51E-02	1.57E-02	3.27E-02
Uterus	7.48E-03	6.89E-03	5.19E-03	3.89E-03
Fetus		6.31E-03	5.03E-03	3.08E-03
Placenta			4.46E-03	3.09E-03
Total Body	3.91E-03	3.89E-03	3.74E-03	3.91E-03
EDE (mSv/MBq)	**1.48E-02**	**1.45E-02**	**1.26E-02**	**1.33E-02**

Dose calculations were performed using the standard MIRD method (MIRD Pamphlet No.1 Society of Nuclear Medicine, 1976). Effective dose equivalents (EDE) were calculated in accordance with ICRP 53 (Ann. ICRP 18 (1-4), 1988) and gave values of 1.48 x 10^{-2} mSv/MBq for female, 1.45 x 10^{-2} mSv/MBq, 1.26 x 10^{-2} mSv/MBq and 1.33 x 10^{-2} mSv/MBq for pregnant women in 3, 6 and 9 months, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

The technetium (^{99m}Tc) labelling reaction involved in preparing technetium (^{99m}Tc) exametazime injection depends on maintaining tin in the divalent (reduced) state. Any oxidant present in the sodium pertechnetate (^{99m}Tc) employed may adversely affect the quality of the preparation. Sodium pertechnetate (^{99m}Tc) 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 obtaining any elute 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 (^{99m}Tc) 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 preservative. 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 (^{99m}Tc) exametazime complex.

Procedure for the Preparation of Technetium Tc99m Exametazime Injection:

Note: Sterile technique must be used throughout. The user should wear waterproof gloves during the handling and administration procedure.

1. Place the vial containing the lyophilised substance in a lead shield.
2. Inject sterile sodium pertechnetate (^{99m}Tc) solution (370-2200 MBq) aseptically in to the vial in a volume of 5 ml. Before removing the syringe, withdraw an equalvolume of the nitrogen gas to normalise the pressure in the vial. (Do not use a breather needle.)
3. Dissolve the lyophilised 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.)
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 ^{99m}Tc-HM-PAO complex should be not 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 ^{99m}Tc-BRAIN-SPECT can determine by this method.

Materials and equipments

1. Saline
2. Chloroform
3. Vortex Mixer
4. Dose calibrator

Procedure

1. Add 0.1 ml of the labelled compound into a vial, which contains 3 ml of chloroform and 2.9ml of saline.
2. Close the vial, mix on a vortex mixer for 1 min., and thereafter wait for separation of phases (1-2 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 ^{99m}Tc-HMPAO is in the chloroform fraction and the contaminants are in the saline layer.
4. Calculation

Calculate the percentage of ^{99m}Tc-BRAIN-SPECT (radiochemical purity):

$$\% \text{ of lipophilic } ^{99m}\text{Tc-BRAIN-SPECT} = \frac{\text{Activity of chloroform fraction}}{\text{Total activity of both fractions}} \times 100$$

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

Method II.

Quality control

Radiochemical purity according to ePh.Eur.: Three potential radiochemical impurities may be present in the prepared exametazime injection. These are a secondary technetium [^{99m}Tc]-exametazime complex, free pertechnetate and reduced-hydrolysed-technetium-99m. A combination of two chromatographic systems is necessary for the determination of the radiochemical purity of the injection.

Materials and equipments

1. 0.9% sodium chloride
2. Methyl ethyl ketone (MEK)
3. TLC silica gel plate R, use a glass-fibre plate (2x20 cm)
4. Tanks
5. suitable counting equipment

Interpretation of Chromatogram

System 1 (TLC: MEK)

- Secondary technetium [^{99m}Tc] exametazime complex and reduced-hydrolysed-technetium remain at the origin.
- Lipophilic technetium [^{99m}Tc] exametazime complex and pertechnetate migrate at Rf 0.8-1.0.

System 2 (TLC: 0.9% sodium chloride)

- Lipophilic technetium [^{99m}Tc] exametazime complex, secondary technetium [^{99m}Tc] exametazime complex and reduced-hydrolysed-Tc 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 µl 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 20cm).
5. The strips are then immediately placed in prepared ascending chromatography development tanks, one containing MEK and the other 0.9% aq. sodium chloride (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 [^{99m}Tc] exametazime complex and reduced-hydrolysed-technetium [^{99m}Tc] from System 1 (A%). Calculate the percentage of activity due to pertechnetate from System 2 (B%).
8. The radiochemical purity (as percentage lipophilic technetium [^{99m}Tc] exametazime complex) is given by:

100-(A%+B%) where: A% represents the level of secondary technetium [^{99m}Tc] exametazime complex plus reduced-hydrolysed technetium-99m
B% represents the level of pertechnetate.

A radiochemical purity of at least 80% may be expected provided the test samples have been taken and analysed within 60 minutes of reconstitution.