1. NAME OF THE MEDICINAL PRODUCT
LEUCO-SCINT kit radiopharmaceutical preparation
Kit for in vitro preparation of Te-99m labelled leukocytes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains:
- active ingredient: Technetium [99mTc]-exametazime
- 0.18 mg

Other ingredients:
For a full list of ingredients see in section 6.1

The product is to be used after reconstitution of the kit and labelling with addition of sterile sodium perchlorate (0.5%) solution for injection.

3. PHARMACEUTICAL FORM
The kit contains 3 vials of lyophilized, sterile, pyrogen free anticoagulant preparation for preparation of Tc-99m-HM-PAO injection, sealed in nitrogen atmosphere used for in vitro labelling of leukocytes. It comprises 3 ampoules of sterile, pyrogen free anticoagulant ACD solution, 3 ampoules of sterile, pyrogen free 6% hydroxyethyl starch (Plasmanate®) plasmacpander and label for the reconstituted product and sanitising swabs (containing 70% isopropyl alcohol) are provided.

4. CLINICAL PARTICULARS
4.1 Diagnostic indications
Technetium [99mTc]-exametazime injection is indicated for in vivo localisation of Te-99m-99mTc-labelled leukocytes to detect or define inflammatory conditions not associated with infection such as inflammatory bowel disease.

4.2 Posology and method of administration
The route of administration is intravenous injection of labelled leukocytes post labelling in vitro.

4.3 Contra-indications
None known.

4.4 Special warnings and special precautions for use
Only qualified person may only be used radiopharmaceutical agent with the appropriate government authorisation for use and manipulation of radionuclides.

4.5 Interaction with other medicinal products and other forms of interaction
Interaction of HM-PAO is not known

Interaction of HM-PAO is not known

Interaction of HM-PAO is not known

4.6 Pregnancy and lactation
Women of childbearing potential should be advised to cease breastfeeding if the administration is considered necessary, breast-feeding should be interrupted for 12 hours and the expressed feeds discarded.

4.7 Effects on ability to drive and use machines
After usage of the drug the ability to drive or operate machines do not influence.

4.8 Undesirable effects
A very few cases of mild hypersensitivity evidences by the development of an arthritic 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 leukocytes prepared using Technetium [99mTc]-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. For most diagnostic investigations using a nuclear medicine procedure the radiation dose (EDR) is less than 1 mSv.

Higher doses may be justified in some clinical circumstances.

4.9 Overdose
In the experiments with the LEUCO-SCINT preparation in rats no signs indicative of toxicity were observed at a dose of 700 mCi Maximum Human Dose.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
At the chemical concentrations and activities used for diagnostic procedures technetium-99m-labelled leukocytes do not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties
Technetium-99m-labelled leukocytes distribute between the marginal pools of the liver (within 5 minutes) and spleen (within about 40 minutes), and the circulating pool, (the latter represents approximately 50% of the whole blood leukocytes). Approximately 37% of the cell-associated activity is removed from the circulation by the liver within 24 hours, and 30% by the kidneys within 24 hours. The remaining 33% is returned to the circulation.

5.3 Preclinical safety data
There are no additional preclinical safety data of relevance for the prescibe in the reconstituting the safety profile of the product used for the authorised indication.

5.4 Special precautions for storage
The kit contains:
- 3 vials of unit dose labelling vials
- 3 vials of 10 mCi ACD-A anticoagulant buffer and
- 3 vials of 14 mCi 6% Hydroxyethyl starch (Plasmanate®) plasmapander

6. INSTRUCTION FOR USE, HANDLING AND DISPOSAL
Any unused product or waste material should be disposed of in accordance with local requirements for radioactive materials.

7. MARKETING AUTHORISATION HOLDER
MEDI-RADIOPHAIRMA LTD.
H-1221 Vadkerti u. 6c.
Tel: 36-23-521-261
Fax: 36-23-521-290
e-mail: mediradiopharma.hu@mediradiopharma.hu

8. MARKETING AUTHORISATION NUMBER
Hungary: OTP/78743/01
Turkey: TR 97/0014
Slovak Republic: 4226/2005
Czech Republic: 88/112/94-C

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORISATION
Date of last renewal: 17. December, 2008

10. DATE OF REVISION TEXT

11. DOSIMETRY
Adult and Children Category
Estimated Absorbed Radiation Dose (Technetium Te-99m Leuco-Scint Injection)

<table>
<thead>
<tr>
<th>Absorbed radiation dose</th>
<th>Target organ</th>
<th>Adult</th>
<th>15 years</th>
<th>10 years</th>
<th>5 years</th>
<th>1 year</th>
<th>Newborn</th>
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<td>2.40E-02</td>
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</tbody>
</table>

Additional information on absorbed radiation doses for the other tissues is available in the CTGR report.
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).

<table>
<thead>
<tr>
<th>Pregnancy Category</th>
<th>Estimated Absorbed Radiation Dose (99m-Tc-Technetium Leuco-Scint Injection)</th>
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</thead>
<tbody>
<tr>
<td>Target organ</td>
<td>Absorbed radiation dose (μGy/MBq)</td>
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<tr>
<td>Adrenals</td>
<td>pT90-Mb</td>
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<tr>
<td>Brain</td>
<td>pT90-Mb</td>
</tr>
<tr>
<td>Breast</td>
<td>pT90-Mb</td>
</tr>
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<td>Gallbladder Wall</td>
<td>pT90-Mb</td>
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<td>LLI Wall</td>
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<td>UlI Wall</td>
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<td>Small Intestine</td>
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<td>Stomach</td>
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<td>Heart Wall</td>
<td>pT90-Mb</td>
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<td>Kidneys</td>
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<tr>
<td>Liver</td>
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<td>Lung</td>
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<td>Muscle</td>
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<td>Fetus</td>
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<td>Placenta</td>
<td>pT90-Mb</td>
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<tr>
<td>Total Body EDE</td>
<td>pT90-Mb (mSv/MBq)</td>
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<tr>
<td>EDE (mSv/MBq)</td>
<td>2.03E-02</td>
</tr>
</tbody>
</table>

12. PROCEDURE FOR SEPARATION AND LABELLING OF LEUCOCYTES

Use aseptic techniques throughout!

1. Draw 2 ml of ACD solution and 3 ml of Plasma and into each of four 20 ml sterile plastic syringes.
2. Withdraw 15 ml of patient’s blood into each syringe and mix gently by inversion.
3. Leave to stand for 30-60 minutes to allow red blood cells to sediment at room temperature.
4. When the red cells have sediment to about half the original volume of the blood, carefully draw up the leucocyte-poorer rich plasma (LPPR) to a sterile (50 ml) tube and centrifuge for 10 minutes at 150 g.
5. Remove the supernatant PRP (plasmat rich plasma) from the pellet of mixed leucocytes leaving the pellet almost dry. Save 10-15 ml of PRP (in 15 ml tube) for step 7. Shake the tube gently to loose the cells.
6. Meanwhile centrifuge the tubes reconstitute one ampoule of LEUCO-SCINT with 1.5 ml of 99m-Tc generator eluate containing 700-750 MBq of 99mTc-pertechnetate. Shake for 10 sec, to dissolve the HM-PAO. The generator eluate must be not more than 2 hours old and the generator previously eluted within the past 24 hours. Add exactly 1 ml of 99mTc-HM-PAO to a tube of mixed leucocytes (the radioactivity of 99mTc-HM-PAO is between 400-500 MBq). Mix gently and incubate the cells for 10 minutes at room temperature.
7. Meanwhile incubate the leucocytes, centrifuge the PRP (step. 5) for 5 minutes (in a 15 ml tube) at 2000 g to produce cell free plasma (CFP).
8. Add 3-5 ml cell free plasma (obtained step. 7.) to the labelled cell suspension and mix.
9. Centrifuge at 150 g for 10 minutes.
10. Transfuse all of the supernatant to a tube (15 ml).
11. Add 3.5 ml of CFP to the pellet of leucocytes, gently swirle to mix.
12. Measure the radioactivity and calculate the labelling efficiency.
13. The labelled leucocytes should be reinjection without delay.

Quality control
1. Viability of separated leucocytes
2. Radiochemical purity measurement of 99mTc-LEUCO-SCINT

Viability
The viability of leucocytes using Trypan-blue colour can determine as follow: mixture of 0.2% Trypan-blue colour: 4.25% sodium chloride solution = 1:1 must add to the suspension of leucocytes. After mild agitation take it in Buret-chamber.

The colour solution can across passively through the destroyed cell membrane so it has blue colour against the native living cells. The viability of cells is expressed in ratio of blue destroyed and native living cells. Using this method more than 90% must be in living form.

Radiochemical purity measurement
1. solvent extraction method
2. chromatographic system

1. Procedure of solvent extraction method
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., then separate the phases for 1-2 min.
3. Transfer the top layer (saline) to another vial and measure the activities of both phases (saline and chloroform) in a dose calibrator. The Phosphate Tc-99m-HM-PAO is in the chloroform fraction and the contaminants are in the saline layer.
4. Calculations

Calculate the percentage of 99mTc-LEUCO-SCINT (radiochemical purity).

Activity of chloroform fraction

% of lipophilic 99mTc-HM-PAO = Activity of chloroform fraction 

Activity of both fractions

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

Leucocytes labelling efficiency not less than 50%.

Interpretation of chromatograms

System 1 (ITLC: butan-2-one/MeOH)
Secondary technetium (99mTc) exametazime complex and reduced-hydrolysed-technetium remains at the origin.
Lipophilic technetium (99mTc) exametazime complex and pertechnetate migrate at Rf 0.8-1.0.
System 2 (ITLC: 0.9% sodium chloride)
Lipophilic technetium (99mTc) exametazime complex, secondary technetium (99mTc) exametazime complex and reduced-hydrolysed-Tc remain at the origin.
Pertechnetate migrates at Rf 0.0-1.0.

The radiochemical purity as percentage lipophilic technetium (99mTc) exametazime complex is given by:

A% represents the level of secondary technetium [99mTc] 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 30 minutes of reconstitution.