1. **NAME OF THE MEDICINAL PRODUCT**

Skeleton 5 mg powder for injection for solution

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Contents of 1 injection vial:

Active substance: Methylene diphosphonic acid (MDP) 5.0 mg

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Kit for radioactive medicinal product. The product is a sterile, pyrogen free lyophilisate, closed in nitrogen atmosphere, and can be labeled in one step with sterile sodium pertechnetate (\(^{99m}\)Tc) solution.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

This medicinal product is for diagnostic use only.

The in vivo diagnostic kit - after being labeled with \(^{99m}\)Tc-pertechnetate sterile solution - is suitable for bone scintigraphic examinations.

4.2 **Posology and method of administration**

Labeling should be performed with a \(^{99m}\)Tc-pertechnetate activity (max. 18.5 GBq) so as to ensure that each patient receives the required 370-740 MBq activity amount at the time of administration.

**Paediatric population**

The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below.

\[
A[\text{MBq}]_{\text{Administered}} = \text{Baseline Activity} \times \text{Multiple}
\]

The baseline activity is 35.0 MBq. The minimum activity for any imaging study is 40 MBq.

<table>
<thead>
<tr>
<th>Weight [kg]</th>
<th>Multiple</th>
<th>Weight [kg]</th>
<th>Multiple</th>
<th>Weight [kg]</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1</td>
<td>22</td>
<td>5.29</td>
<td>42</td>
<td>9.14</td>
</tr>
<tr>
<td>4</td>
<td>1.14</td>
<td>24</td>
<td>5.71</td>
<td>44</td>
<td>9.57</td>
</tr>
<tr>
<td>6</td>
<td>1.71</td>
<td>26</td>
<td>6.14</td>
<td>46</td>
<td>10.00</td>
</tr>
<tr>
<td>8</td>
<td>2.14</td>
<td>28</td>
<td>6.43</td>
<td>48</td>
<td>10.29</td>
</tr>
<tr>
<td>10</td>
<td>2.71</td>
<td>30</td>
<td>6.86</td>
<td>50</td>
<td>10.71</td>
</tr>
<tr>
<td>12</td>
<td>3.14</td>
<td>32</td>
<td>7.29</td>
<td>52-54</td>
<td>11.29</td>
</tr>
<tr>
<td>14</td>
<td>3.57</td>
<td>34</td>
<td>7.72</td>
<td>56-58</td>
<td>12.00</td>
</tr>
<tr>
<td>16</td>
<td>4.00</td>
<td>36</td>
<td>8.00</td>
<td>60-62</td>
<td>12.71</td>
</tr>
<tr>
<td>18</td>
<td>4.43</td>
<td>38</td>
<td>8.43</td>
<td>64-66</td>
<td>13.43</td>
</tr>
<tr>
<td>20</td>
<td>4.86</td>
<td>40</td>
<td>8.86</td>
<td>68</td>
<td>14.00</td>
</tr>
</tbody>
</table>
Course of examination:
The patient receives $^{99m}$Tc-Skeleton as intravenous injection. Bone scintigraphy (whole body or targeted test, or SPECT test - should be started 2-4 after administration. Gamma camera (or scanner) imaging is performed after administration.

4.3 Contraindications

Hypersensitivity to the active ingredient(s) or to any excipient of the medicinal product. In case of pregnant or breastfeeding mothers (see section 4.6), except when the likely benefit far exceeds the risk.

4.4 Special warnings and precautions for use

If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

The administration of ionizing radiation for each patient should be supported by the advantages of its use.
The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

The applied radiation dose (effective dose/EDE) used in case of the majority of diagnostic tests performed with nuclear medicinal methods is lower than 20 mSv. Administering doses higher than this is justified only under certain clinical circumstances.

The product is a medicinal product that contains radioisotope. With regards to the handling, shipment and storage of the medicinal product rules for radioactive substances apply.
The medicinal product can only be administered in designated clinical units with special authorization for using radioisotopes, and by individuals with special training certificates.

The radiopharmacon should be administered with special caution so as to minimize the radiation dose for the patient and the clinical staff.
The radiopharmacon to be administered to the patient should be prepared in compliance with safety and pharmaceutical quality requirements for radioactive substances. Principles of GMP must be adhered to on a compulsory basis; aseptic conditions must be maintained.

Radiation protective requirements must be adhered to during the labeling procedure and administration. In order to mitigate bladder-irritation adequate fluid intake and frequent urination is necessary.

In case of renal failure exposure to ionizing radiation can increase, and this should be considered when the activity to be applied is calculated.

4.5 Interaction with other medicinal products and other forms of interaction

Possible interactions:
Accumulation of the radioactive substance is increased in the bones by:
- ferrous compounds
- chemotherapeutic agents and immunosuppressants
- Aluminum containing acid reducers
- x-ray contrast agents
- antibiotics, anti-inflammatory agents
- Calcium gluconate injection
4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

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 breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 24 hours and the expressed feeds discarded. Breastfeeding can start if the level of radioactivity in mother’s milk would not exceed 1 mSv for the fetus.

4.7 Effects on ability to drive and use machines

Administration of the radiopharmacon does not influence the ability to drive or use machines.

4.8 Undesirable effects

| Congenital, inherited and genetic abnormalities | inherited defect |
| Diseases and symptoms of the nervous system | headache |
| Gastrointestinal diseases and symptoms | vomiting |
| Diseases and symptoms of the musculoskeletal system and connective tissues | arthralgia |
| Benign, malignant and undefined tumours (including cysts and polyps) | tumour induction |
| Surgical and other medical interventions and procedures | subepidermal vasodilatation |
| Vascular diseases and symptoms | blood pressure decrease and low blood pressure, nausea |
| General symptoms and administration site reactions | hypersensitivity reactions, local or general itchy rashes, weakness and oedema of the extremity |
The dose caused by the ionizing radiation should be justifiable for each patient with the useful information gained from the test. The given activity should be selected so as to achieve the desired diagnostic result with the lowest possible radiation dose.

Ionizing radiation can be carcinogen and may lead to the development of inherited abnormalities. Based on generally accepted evidence such undesirable effects only rarely develop during isotope diagnostic tests due to the low radiation dosages applied.

Most of the diagnostic tests using nuclear medicinal procedures operate with a radiation dose (EDE) lower than 20 mSv.

4.9 Overdose

No information is available for overdosing. Should this happen however, activities should primarily aim at maintaining the patient's vital functions.

The administration of radioactivity higher than required causes unnecessary radiation exposure for the patient and his/her environment, thus it should be avoided. Should this still happen by medical staff error, the actually administered value of $^{99m}$Tc activity should be established in MBq, and the absorbed dose corresponding to the individual organs and the whole body must be calculated based on the dosimetric table provided under section 11. Based on the values obtained, a decision should be made whether the patient should be assigned to radiomedical procedure-treatment. The table includes absorbed dose values expressed in µGy caused during the intravenous administration of 1 MBq $^{99m}$Tc-Skeleton; and this should be multiplied by the administered activity expressed in MBq to obtain the absorbed dose values in µGy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: radiopharmacons used in diagnostics, ATC code: V09BA02

In the chemical concentration used during diagnostic tests and having that radioactivity, the [$^{99m}$Tc]-technetium-medronate shows no pharmacodynamic effect.

5.2 Pharmacokinetic properties

Distribution:
After intravenous administration $^{99m}$Tc-methylene-diphosphonate eliminates from blood, and is mainly taken up by the skeletal system, and almost to a negligible extent by soft tissues. The extent of bone uptake peaks 1-2 hours after administration, and remains stable for approx. 72 hours. A significantly lower portion of $^{99m}$Tc-methylene diphosphonate binds to proteins in the blood plasm, and this results in only a very limited body background.

Radiation doses absorbed in critical organs in healthy subjects are detailed under section 11.

Elimination:
Intravenously administered $^{99m}$Tc-methylene-diphosphonate is eliminated from blood in 3 phases:
- Fast phase $T \frac{1}{2} = 3.5$ minutes
- Moderate phase $T \frac{1}{2} = 27$ minutes
- Slow phase $T \frac{1}{2} = 144$ minutes

During the fast phase $^{99m}$Tc-Skeleton is released from the blood into the extravascular space, while the moderate phase corresponds to bone uptake. During the slow phase plasmaprotein-bound $^{99m}$Tc-Skeleton gets dissociated in blood.

$^{99m}$Tc-Skeleton is excreted with urine; excretion through the hepatobiliar system is generally negligible. Activity in the kidneys peaks 20 minutes after administration. In case of normal kidney functions 32%
of the total administered activity is filtered glomerularly, the 47% of which presents in the urine within 2 hours, and 60% presents in the urine within 6 hours.
Unique factors influencing pharmacokinetics:

As a general experience, 50% of the injected $^{99m}$Tc-Skeleton activity is absorbed by the skeletal system. In healthy subjects this value usually does not exceed 31%.

In case of bone metastases, almost 40% of the injected activity accumulates exclusively in the metastases, thus metastases significantly differ from the picture of the skeletal system (bones). The same applies for fractures, inflammations, and for cases of hyperparathyroidism and osteoporosis. Mechanism of uptake: ion-exchange and chemisorption in the inorganic matrix of the bone, i.e. in the hydroxil-apatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) of ionic nature. Phosphate groups on the bone matrix surface enter into an ion-exchange reaction with the free $\text{PO}_3\text{H}_2$ groups of medronate coordinated to technetium, and as a result, $^{99m}$Tc activity is bound on the bone matrix. The same process takes place in normal bone as well, however, binding is more significant where the bone’s blood supply and bone restructuring activity (osteoblast activity) is increased.

Thus an increased $^{99m}$Tc activity can be observed on the site of bone lesions (primary tumours, metastases, and certainly bone clefts, fractures and inflammations) that allows for imaging of deviations.

5.3 Results of preclinical safety studies

According to the intravenous acute toxicity study performed on mice no clinical symptom can be experienced up to a dose of 9 mg/body weight kgs. During prescription compliant dosaging each patient is exposed to a minimum of 0.5 mg and a maximum of 1.66 mg $^{99m}$Tc-Skeleton.

No studies were performed with regards to chronic toxicity, mutagen potential, toxicity on the reproductive system and carcinogen potential of the product, the reason for this being the clinical use of the product (the usual necessary dose is a single intravenous dose in the magnitude of mgs).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tin(II)-chlordie-dihydrate, Sodium-pyrophosphate decahydrate, L-ascorbic acid.

6.2 Incompatibilities

Injection vials of the Skeleton radioactive kit contain reducing tin(II)-chloride that forms technetium with a degree of oxidation (+4) capable for complex formation from free pertechnate (+7). The content of the injection vials is therefore incompatible with humidity and oxidizing media (chemical oxidizers, oxygen content in the air, etc). The substance is incompatible with any alkali, since the alkaline media facilitates tin(II) oxidation before the radioactive labeling process is executed. Therefore the protecting cap of the closed injection vials should be opened only directly before the radioactive labeling process, and radioactive labeling should be performed according to specifications regarding product use/handling.

6.3 Shelf-life

The kit (lyophilized non-radioactive components in injection vial closed with a rubber-stopper and aluminum cap) can be used for 2 years after manufacturing in unopened packaging until the date indicated on the kit packaging. Labeled product should be used within 8 hours after labeling.

6.4 Special precautions for storage

Store below 25°C. Keep protected from oxidizers. Labeled product can be stored below 25°C.
During storage of the labeled product effective protection and safety regulations should be adhered to. The contents of the injection vial included in the kit may only be used for the production of $^{99m}$Tc-technetium labeled injection, according to the summary of product characteristics.

The radiopharmacon can only be used by a physician or an adequately trained individual experienced in radionuclide treatment and in adherence to effective protective and safety regulations.

6.5 Type of packaging

According to the specifications of the European Pharmacopoeia type I sterile, transparent, 8 mL volume injection vial with a sterile siliconized chlorbutyl rubber stopper closed with a sterile plastic-aluminium flip-off cap. Labeled vials are packaged into boxes. One box contains 6 injection vials.

6.6 Special precautions on destruction and other information on the use of the product

The destruction of any unused product and waste should be performed according to local regulations.

7. MARKETING AUTHORISATION HOLDER

Name: MEDI-RADIOPHARMA Ltd.
Address: 2030 Érd Szamos u. 10-12.
Telephone: 06-23-521-261
Fax: 06-23-521-260
e-mail: mediradiopharma-kft@mediradiopharma.hu

8. MARKETING AUTHORISATION NUMBER(S)

R00095

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2016 October

10. DATE OF REVISION OF THE TEXT

2016 October

11. EXPECTED RADIATION EXPOSURE

The following table shows radiation doses absorbed by healthy individuals as referred to the administered dose of $[^{99m}]$Tc-phosphate and phosphonate dose, according to e ICRP-80 (International Committee of Radiation Protection):

<table>
<thead>
<tr>
<th>Organs</th>
<th>Absorbed dose referred to a unit of administered activity (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>adult</td>
</tr>
<tr>
<td>adrenal</td>
<td>0.0021</td>
</tr>
<tr>
<td>bladder</td>
<td>0.048</td>
</tr>
<tr>
<td>bone surface</td>
<td>0.063</td>
</tr>
<tr>
<td>brain</td>
<td>0.0017</td>
</tr>
<tr>
<td>breast</td>
<td>0.00071</td>
</tr>
<tr>
<td>gall bladder</td>
<td>0.0014</td>
</tr>
<tr>
<td>gastrointestinal system</td>
<td></td>
</tr>
<tr>
<td>stomach</td>
<td>0.0012</td>
</tr>
<tr>
<td>small intestines</td>
<td>0.0023</td>
</tr>
<tr>
<td>large intestine</td>
<td>0.0027</td>
</tr>
<tr>
<td>Tissue</td>
<td>Effective dose equivalent (mSv/MBq)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>upper portion of the large intestine</td>
<td>0.0019</td>
</tr>
<tr>
<td>lower portion of the large intestine</td>
<td>0.0038</td>
</tr>
<tr>
<td>heart</td>
<td>0.0012</td>
</tr>
<tr>
<td>kidneys</td>
<td>0.0073</td>
</tr>
<tr>
<td>liver</td>
<td>0.0012</td>
</tr>
<tr>
<td>lung</td>
<td>0.0013</td>
</tr>
<tr>
<td>muscles</td>
<td>0.0019</td>
</tr>
<tr>
<td>oesophagus</td>
<td>0.0010</td>
</tr>
<tr>
<td>ovaries</td>
<td>0.0036</td>
</tr>
<tr>
<td>pancreas</td>
<td>0.0016</td>
</tr>
<tr>
<td>red bone marrow</td>
<td>0.0092</td>
</tr>
<tr>
<td>skin</td>
<td>0.0010</td>
</tr>
<tr>
<td>spleen</td>
<td>0.0014</td>
</tr>
<tr>
<td>testis</td>
<td>0.0024</td>
</tr>
<tr>
<td>thymus</td>
<td>0.0010</td>
</tr>
<tr>
<td>thyroid gland</td>
<td>0.0013</td>
</tr>
<tr>
<td>uterus</td>
<td>0.0063</td>
</tr>
<tr>
<td>other tissues</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

In case of a healthy adult assuming a 70 kg body weight the effective dose equivalent after administering 740 MBq activity is typically 4.2 mSv. In case of 740 MBq administered activity the effective dose is equivalent is 46.6 mGy for the target organ (bone), and is 35.5 mGy for the critical organ (bladder wall).

**12. GUIDANCE ON THE PREPARATION OF RADIOPHARMACONS**

The skeleton in vivo kit cannot be used directly as an injection; only the $^{99m}$Tc-Skeleton - that is formed after radionuclide labeling is completed - can be administered to the patient. One should take into account that $^{99m}$Tc-Skeleton is a solution containing radioactive isotopes, so when it is produced and used, regulations on radiating substances should also be adhered to in addition to pharmaceutical requirements.

**Labeling**

Place the injection vial containing the lyophilizate into a lead capsule of 3 mm thick walls, then under aseptic conditions inject the sterile $^{99m}$Tc-pertechnetate of desired activity (max 18.5 GBq) through the rubber stopper into the vial (volume 1-5 ml). Before pulling the needle out of the vial, take out 1-5 cm$^3$ nitrogen gas from the vial into the syringe to even out the pressure. Do NOT use breather needles! Shake the vial until the lyophilizate is solved, let it stand for 15 minutes below 25°C, and periodically and repeatedly shake the vial again. Complete the attached label and stick it on the preparation. pH of labeled preparation: 3.7 – 7.5 (Ph.Eur. 6.0)

The labeled preparation should be used within 8 hours after the time of labeling. During this period the amount of radiochemical impurities cannot exceed 5%.
Quality control
Radiochemical purity

Detection of reduced, hydrolized $^{99}$mTc with thin layer chromatography

1. Drop 5-5 µl of the test solution 2 cm distance from one end of the band on the 2 silicagel layers pre-treated for 10 minutes at 110°C (size:2.0x20 cm).
2. Develop chromatograms with sodium-acetate eluent (136g/l) to 10 cm front distance.
3. After development dry the silicagel layers. Detection is performed with a radioactivity detector.
4. Reference Rf values:
   - technetium-medronate-complex + free pertechnetate: Rf = 0.9 – 1.0
   - hydrolyzed technetium + colloid impurity: Rf = 0.0 – 0.1

Requirement: the amount of hydrolyzed and colloid technetium together with the pertechnetate ion: max 5%.

Determination of free pertechnetate with thin layer chromatography

1. Drop 5-5 µl of the test solution 2 cm distance from one end of the band on the 2 silicagel layers pre-treated for 10 minutes at 110°C (size:2.0x20 cm).
2. Develop chromatograms with methyl-ethyl keton eluent to a 10 cm front distance.
3. After development dry the silicagel layers. Detection is performed with a radioactivity detector.
4. Reference Rf values:
   - free pertechnetate: Rf = 0.9 – 1.0
   - labeled complex + technetium colloid: Rf = 0.0 – 0.1

The amount of free pertechnetate cannot exceed 2%.