1. **NAME OF THE MEDICINAL PRODUCT**

**Meta-Iodobenzylguanidine-**\(^{131}\)I (MIBG-\(^{131}\)I) for diagnostic use, solution for injection

2. **QUANTITATIVE AND QUALITATIVE COMPOSITION**

Meta-Iodo(\(^{131}\)I)benzylguanidine sulphate, 10 - 37 MBq/ml

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Meta-Iodobenzylguanidine-\(^{131}\)I (MIBG-\(^{131}\)I) is a diagnostic radiopharmaceutical for gamma-scintigraphy.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

- **Pharmaceutical group:** diagnostic radiopharmaceutical

- **Therapeutic use:** includes the use of iodine-based contrast (radiological examinations), excess iodine in a patient's diet (e.g., multivitamin preparations), thiourea derivatives (propylthiouracil, methimazole), imidazol derivatives, amiodarone.

- **Inhibition of accumulation of MIBG-**\(^{131}\)I and other forms of interaction

- **4.2 Posology and method of administration**

- **Posology depends on the type of examination.** In diagnostic examinations, the radiopharmaceutical is slowly administered intravenously (over approximately 30 seconds). In scintigraphic imaging of pheochromocytoma, the recommended dose for adults is 18.5 MBq - 37 MBq. The scintigraphic examination should be performed after 24, 48 and 72 hours after administration of the radiopharmaceutical. As a method facilitating the interpretation of the scintigraphic image, it is recommended that the MIBG-\(^{131}\)I image is superimposed on the image of the kidneys, obtained after administering \(^{99m}\)Tc-MDP. Since the pheochromocytoma can be found outside of the kidneys in 10 - 15% of all cases, it is recommended to perform the whole body scan.

6. **CONTRAINDICATIONS**

An absolute contraindication to use the preparation is pregnancy and breastfeeding.

A relative contraindication is age below 10 years.

7. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

- **Before conducting an examination using MIBG-**\(^{131}\)I it is vital to block the thyroid. This can be done via the administration of iodine solutions, such as the Lugol's solution, in amounts equivalent to 40 mg of iodine per day, for 7 days, starting 3 days before administering the radiopharmaceutical, and for three days following its administration.

- **Potassium perchlorate** may also be used for blocking the thyroid.

- **Radiopharmaceuticals may only be used in authorized facilities and by authorized persons.**

- **Safety precautions for careful handling this radiopharmaceutical should be observed.** Ensure protection of the staff and patients against unnecessary exposure to ionising radiation. Permit to store and administer radiopharmaceuticals depends on specified local standards and regulations for radioactive materials.

- **Patients exposed to high doses of radioisotope** \(^{131}\)I need to be hospitalized because of high radiological risk.

8. **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**

- **Labeletalol, reserpine, tricyclic antidepressants and sympathicomimetics inhibit the accumulation of MIBG-**\(^{131}\)I in pheochromocytoma. They should be laid off within 7-14 days prior to the examination.

- **The uptake of the agent by the thyroid can be reduced by:**
  - excess iodine in a patient's diet (e.g., multivitamin preparations)
  - use of iodine-based contrast (radiological examinations)
  - steroid hormones, thyroid hormones (triiodothyronine, thyroxine),
  - bromides, nitrates, perchlorates, thiocyanides, iodides (Lugol’s solution), sulphonamides, thiourea derivatives (propylthiouracil, methylthiouracil), imidazol derivatives, amiodarone.

- **Administration of TSH** (thyroid-stimulating hormone) leads to an increase of iodine uptake by the thyroid gland. Taking into account all these factors, the physician should be aware of the previous treatment history of the patient.

9. **PREGNANCY AND LACTATION**

- **When it is necessary to administer radiopharmaceuticals to women of childbearing potential information should always be sought about pregnancy.** Pregnancy should be excluded in any women who has had menstrual cycle disturbances. Any women who has missed a period should be assumed to be pregnant until proven otherwise. Examinations using radiopharmaceuticals in women of childbearing potential should be carried out during the first (about 10) days following the onset of menses.

- **Breastfeeding should be interrupted following administration of the first dose of radiopharmaceutical product due to potential risk for the child.** It can be restarted when radiation dose potentially received by the child during breastfeeding and contact with mother is within the range of approved standards. Where uncertainty exists it is important to minimize the radiation exposure during examinations. Alternative techniques which do not involve ionising radiation should be considered.

10. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

  - **MIBG-**\(^{131}\)I does not affect the ability to drive or to use machines.

11. **UNDESIRABLE EFFECTS**

- **The exposure to ionising radiation may be connected with the risk of induction of neoplasm development or it may result in 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 examinations used in nuclear medicine, the absorbed dose is lower than 20 mSv.

- **Radiation caused by the diagnostic radiopharmaceutical has insignificant carcinogenic and mutagenic effect, while therapeutic doses carry a greater risk.**

- **Administration of the MIBG-**\(^{131}\)I in a diagnostic dose may sometimes cause nausea, rash, itching, urticaria, flushing and other minor allergic reactions.

- **An iodine intolerance reaction may be caused by administration of MIBG-**\(^{131}\)I and other agents containing iodide.

12. **OVERDOSE**

- **The product is delivered in the form of a solution, in vials of declared activity, which allows the responsible physician better supervision on the dose administrated to the patient.** Should an accidental administration of an excess of radioactive substance occur, the radiation risk to the patient can be reduced by providing liquids and induction of frequent voiding.

13. **PHARMACOLOGICAL PROPERTIES**

**MIBG-**\(^{131}\)I is a radiiodinated aralkylguanidine. Its structure contains the guanidine-group from guanethidine linked to a benzyl-group into which iodine is introduced. Like guanethidine, the aralkylguanidines are adrenergic neuron blocking agents.

14. **1. PHARMACODYNAMIC PROPERTIES**

**MIBG-**\(^{131}\)I is a radiiodinated aralkylguanidine. Its structure contains the guanidine-group from guanethidine linked to a benzyl-group into which iodine is introduced. Like guanethidine, the aralkylguanidines are adrenergic neuron blocking agents.

15. **1. PHARMACOKINETIC PROPERTIES**

**Clinical tests have shown that administration of 1 mg of labeled meta-
iodobenzylguanidine in humans does not cause any effects from the sympathetic nerve system. The liver, the spleen and salivary glands have a high affinity for MIBG-\(^{131}\)I. Activity has also been noted in the heart area and lower sections of the lungs. Normal adrenal glands absorb MIBG-\(^{131}\)I only slightly. Over 60% of the administered MIBG-\(^{131}\)I is excreted with urine after 24 hours.

5.3 Preclinical safety data
The L\(_{D_{0.1}}\) value of methylbenzylguanidine after intravenous administration of non-radioactive substance is 30 mg/kg of mice body mass.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
meta-iodobenzylguanidine sulphate
sodium metabisulphite
copper (II) sulphate pentahydrate
sodium acetate trihydrate
acetic acid
benzyl alcohol
sodium chloride
water for injection

6.2 Incompatibilities
No data.

6.3 Shelf life
9 days from the manufacturing date (expiry date is stated on the label).

6.4 Special precautions for storage
Store MIBG-\(^{131}\)I in original container at the temperature below \(-15\)\(^\circ\)C in accordance with regulations for radiation safety. Protect from light. After defrosting store below 25\(^\circ\)C for up to 4 hours. Transport in dry ice.

6.5 Nature and contents of container
The MIBG-\(^{131}\)I solution is delivered in 10 ml glass vials, with a possibility of drawing multidoses in an aseptic way. The vials are capped with rubber stoppers and aluminium caps and placed inside a lead shielding container. The outer transport packaging is a metal tin with styrofoam insert.

6.6 Special precautions for disposal
This radiopharmaceutical may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the local competent official organizations. Any unused products and material waste should be disposed of in accordance with regulations for radioactive materials.

7. MARKETING AUTHORISATION HOLDER
National Centre for Nuclear Research
Andrzej Sołtan 7, 05-400 Otwock, Poland
Phone:  +48 22 7180700
Fax:  +48 22 7180350
e-mail: polatom@polatom.pl

8. MARKETING AUTHORISATION NUMBER(S)
19000

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30.03.2001 / 11.08.2005 / 27.03.2006 / 29.01.2007/21.11.2008

10. DATE OF APPROVAL/REVISION OF THE TEXT
31.10.2011

11. DOSIMETRY
The half-life of I-131: 8.02 days
After administering MIBG-\(^{131}\)I, the following radiation doses can be expected to be absorbed by various organs, depending on the patient’s age: ICRP 53 (Vol.18 - No 1-4, 1987) „Radiation dose to patients from radiopharmaceuticals”.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Adults</th>
<th>15-year</th>
<th>10-year</th>
<th>5-year</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.17</td>
<td>0.23</td>
<td>0.33</td>
<td>0.45</td>
<td>0.69</td>
</tr>
<tr>
<td>Bladder wall</td>
<td>0.59</td>
<td>0.73</td>
<td>1.1</td>
<td>1.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.061</td>
<td>0.072</td>
<td>0.11</td>
<td>0.18</td>
<td>0.36</td>
</tr>
<tr>
<td>Breast</td>
<td>0.069</td>
<td>0.069</td>
<td>0.11</td>
<td>0.18</td>
<td>0.35</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach wall</td>
<td>0.077</td>
<td>0.093</td>
<td>0.15</td>
<td>0.25</td>
<td>0.47</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.074</td>
<td>0.091</td>
<td>0.15</td>
<td>0.24</td>
<td>0.45</td>
</tr>
<tr>
<td>ULI wall</td>
<td>0.08</td>
<td>0.096</td>
<td>0.16</td>
<td>0.26</td>
<td>0.48</td>
</tr>
<tr>
<td>LLI wall</td>
<td>0.068</td>
<td>0.081</td>
<td>0.13</td>
<td>0.21</td>
<td>0.39</td>
</tr>
<tr>
<td>Heart</td>
<td>0.072</td>
<td>0.091</td>
<td>0.14</td>
<td>0.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.12</td>
<td>0.14</td>
<td>0.21</td>
<td>0.3</td>
<td>0.51</td>
</tr>
<tr>
<td>Liver</td>
<td>0.83</td>
<td>1.1</td>
<td>1.6</td>
<td>2.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.19</td>
<td>0.28</td>
<td>0.39</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.066</td>
<td>0.088</td>
<td>0.14</td>
<td>0.23</td>
<td>0.42</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.1</td>
<td>0.13</td>
<td>0.2</td>
<td>0.32</td>
<td>0.57</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>0.23</td>
<td>0.28</td>
<td>0.38</td>
<td>0.51</td>
<td>0.75</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.067</td>
<td>0.083</td>
<td>0.13</td>
<td>0.19</td>
<td>0.35</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.49</td>
<td>0.69</td>
<td>1.1</td>
<td>1.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Testes</td>
<td>0.059</td>
<td>0.07</td>
<td>0.11</td>
<td>0.19</td>
<td>0.36</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.05</td>
<td>0.065</td>
<td>0.11</td>
<td>0.18</td>
<td>0.35</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.08</td>
<td>0.1</td>
<td>0.16</td>
<td>0.26</td>
<td>0.48</td>
</tr>
<tr>
<td>Other tissues</td>
<td>0.062</td>
<td>0.075</td>
<td>0.12</td>
<td>0.19</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Effective dose equivalent \([\text{mSv/MBq]}\): 0.2 \(\text{mSv/MBq}\)

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
The radiopharmaceutical is supplied in portions containing required activity (certified on 12.00 CET of the reference day). During handling and administration the measures for radiation protection of the personnel must be strictly observed.

Handling procedure
1. Tear off the seal of the metal tin.
2. Remove the upper styrofoam insert.
3. Take the lead container out of the box and place it in the working area.
4. Open the lead shielding container.
5. Without removing the vial from the container, remove or tear of the central part of the aluminum cap.
6. Pierce the rubber septum with a needle and draw the solution to the syringe.
7. Any materials contaminated with the radioactive product: liquid leftovers of the radiopharmaceutical and solid (vials, stoppers, needles, syringes, paper, cotton wool, etc.) should be stored in separate, securely sealed containers and should be disposed of in accordance to local regulations.
8. The shielding container should be returned to the manufacturer.

When drawing the radiopharmaceutical and administering it to the patient, work safety regulations for working under exposure to ionising radiation should be observed.

Any unused products and material waste should be disposed of in accordance with regulations for radioactive materials.

MIBG-\(^{131}\)I Quality control
Determine the radiochemical purity using the thin-layer chromatography in the following system:
Plate: silica gel (Kieselgel 60, Merck 5748)
Developing solution: 13.6% solution of sodium acetate.
\(R_f\) coefficients:
- MIBG-\(^{131}\)I \(R_f = 0.15\)
- unbound \(^{131}\)I \(R_f = 0.90\)