1. NAME OF THE MEDICINAL PRODUCT

Meta-Iodobenzylguanidine-\textsuperscript{131}I (MIBG-\textsuperscript{131}I) for therapeutic use, solution for injection

2. QUANTITATIVE AND QUALITATIVE COMPOSITION

Meta-Iodo[\textsuperscript{131}]benzylguanidine sulphate, 370 - 740 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-\textsuperscript{131}I (MIBG-\textsuperscript{131}I) is a radiochemical used in cancer therapy. It is used in treating disseminated, malignant, metastatic lesions, such as pheochromocytoma, paraganglioma, neuroblastoma, neuroendocrine tumors of gastroenteropancreatic tract, and sometimes medullary thyroid carcinoma.

4.2 Posology and method of administration

In cancer therapy using the MIBG-\textsuperscript{131}I the recommended single dose is approximately 3.7 GBq. The therapeutic dose should be diluted with saline to a volume of approximately 50 ml and administered intravenously within 1.5 - 2 hours. The recommended dose is the same for adults and children.

4.3 Contraindications

An absolute contraindication to use the preparation is pregnancy and breastfeeding. A relative contraindication is age below 10 years.

4.4 Special warnings and precautions for use

Before conducting an examination using MIBG-\textsuperscript{131}I it is necessary 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 the administration. Potassium perchlorate may also be used for blocking the thyroid. Radiopharmaceuticals may be used only by authorized persons in designated clinical settings. 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 radiisotope \textsuperscript{131}I need to be hospitalized because of high radiological risk.

4.5 Interaction with other medicinal products and other forms of interaction

Labetalol, reserpine, tricyclic antidepressants and sympathicomimetics inhibit the accumulation of MIBG-\textsuperscript{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)
- the use of iodine-based contrast (radiological examinations)
- steroid hormones, thyroid hormones (triiodothyronine, thyroxine), bromides, nitrates, perchlorates, thiocyanates, iodides (Lugol’s solution), sulphonamides, thio-eye 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.

4.6 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. Pregnancy should be avoided for 1 year following the treatment. 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.

4.7 Effects on ability to drive and use machines

The radiopharmaceutical has no influence on ability to drive and use machines.

4.8 Undesirable effects

The activity of the administered radiopharmaceutical dose should always be considered in relation to its diagnostic and therapeutic benefits. This is especially relevant to therapeutic doses which may cause serious side effects. Very seldom the administration of the MIBG-\textsuperscript{131}I may cause nausea, rash, itching, urticaria, flushing and other minor allergic reactions. In case of therapeutic doses the minor side effects listed above may be accompanied with side effects related to radiotoxicity. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.

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

4.9 Overdose

The product is delivered in the form of solution with declared radioactivity, which allows the responsible physician better supervision on the dose administered 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.

5. PHARMACOLOGICAL PROPERTIES

MIBG-\textsuperscript{131}I is a radioiodinated 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.

5.1 Pharmacodynamic properties

Pharmaceutical group: diagnostic radiopharmaceutical

ATC code: V 10X A02

Of the various aralkylguanidines meta-iodobenzylguanidine is the preferred substance because of its lowest liver uptake and its best in vivo stability, resulting in the lowest achievable uptake of liberated iodide by the thyroid.

Transport of MIBG-\textsuperscript{131}I across the cell membranes of cells originating from the neural crest is an active process when the concentration of the drug is low (as in diagnostic dosages). The uptake mechanism can be inhibited by uptake of inhibitors such as cocaine or desmethylimipramine. When the drug is administered in higher concentrations (as in therapeutic dosages) passive diffusion processes become also important. Subsequently an active mechanism transfers at least part of the intracellular meta-iodobenzylguanidine into the storage granules within the cells.

5.2 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-\textsuperscript{131}I. Activity has also been noted in the heart area and lower sections of the lungs. Normal adrenal glands absorb MIBG-\textsuperscript{131}I only slightly. Over 60% of the administered MIBG-\textsuperscript{131}I is excreted with urine after 24 hours.
5.3 Preclinical safety data
The LD₅₀ value of inactive methylobenzyloguanidine in intravenous administration is equal 30 mg/kg of mice body mass.

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

6.2 Incompatibilities
- Not known.

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

6.4 Special precautions for storage
Store MIBG-[¹³¹I] in an original container at the temperature below [-15°C], in accordance with regulations for radiation safety. Transport in dry ice. Protect from light. After defrosting store below 25°C for up to 2 hours. Transport in dry ice.

6.5 Nature and contents of container
The MIBG-[¹³¹I] 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 aluminum caps and placed inside a shielded lead container. The outer transport packaging is a metal tin with styrofoam insert. Every source is accompanied with a certificate of radioactivity.

6.6 Special precautions for disposal
Any unused products and material waste should be disposed in accordance with regulations for radioactive materials.

7. MARKETING AUTHORISATION HOLDER
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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)
8711

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30.03.2001/11.08.2005/27.03.2006/29.01.2007/28.10.2008

10. DATE OF REVISION/PARTIAL REVISION OF THE TEXT
31.10.2011

11. DOSIMETRY
The half-time of I-131: 8.02 days
After administering MIBG-[¹³¹I], 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 [mSv/MBq] 0.2 0.26 0.4 0.61 1.1

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
The radiopharmaceutical is delivered 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 part of the 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 off 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 solids (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.

During the preparation and administration of the radiopharmaceutical, regulations for work under exposure to ionising radiation should be observed.
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-[¹³¹I] Quality control
Determination of the radiochemical purity using thin-layer chromatography in the following system:
- Plate: silica gel (Kieselgel 60, Merck 5748)
- Developing solution: 13.6% solution of sodium acetate
- Developing solution: 13.6% solution of sodium acetate

R₂ coefficients:
- MIBG-[¹³¹I] R₂ = 0.15
- unbound [¹³¹I] R₂ = 0.90

POLATOM