2.3 Radioactive properties

2.3.1 Specific activity
Not less than 5 GBq/mg.

2.3.2 Activity concentration
2500 MBq/ml.

2.3.3 Radioactivity purity at the time of utilisation
> 99.9%

2.3.4 Radiochemical purity
> 95%

2.4 PHARMACEUTICAL FORM

Pharmaceutical form of MULTIBONE in vivo kit: powder for solution for injection.

Pharmaceutical form of 153Sm-samarium chloride precursor: sterile solution not used directly as pharmaceutical preparation.

Pharmaceutical form of 153Sm-MULTIBONE: injectable, radioactive, sterile injection.

2.5 CLINICAL PARTICULARS

4.1 Indications

INDICATION FIELD: RADIONUCLIDE THERAPY

Palliative, diagnostic treatment of previously localized bone metastases. Use of the preparation highly recommended in case of the indications listed below:

- palliative treatment of painful bone metastases of breast cancer
- palliative treatment of bone metastases of prostate cancer
- palliative treatment of bone metastases of other tumours

4.2 Polochemistry and method of administration

153Sm-Multibone is prepared in one labelling reaction representing a dose for one patient. Labelling should be performed by using 2500 MBq of 153Sm. The individual patient dose is 2500 MBq of 153Sm-Multibone.

4.2.1 Method of administration

153Sm-Multibone should be administered slowly, intravenously to the patient. After this, the patient should drink 100 ml/10 kg of bodyweight of water. In case of administration of the recommended dose the administered quantity per volume unit

25.0 mg Organ-specific radiolabeling agent of 152Sm radium chloride precursor

Excipients

Stannous chloride dihydrate

1.0 mg Promoter of the formation of the complex

Ascorbic acid

5.0 mg Stabiliser

Glucose, anhydrous

10.0 mg Filter

2.1.2 Composition of 153Sm/samarium chloride precursor

Table of the components

<table>
<thead>
<tr>
<th>Name of the components</th>
<th>Quantity per volume unit</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>153Sm-samarium chloride</td>
<td>2500 MBq</td>
</tr>
<tr>
<td>Excipients</td>
<td>Sodium chloride</td>
<td>9 mg</td>
</tr>
<tr>
<td></td>
<td>Water for injection</td>
<td>1 ml</td>
</tr>
</tbody>
</table>
| 2.1.3 Composition of 153Sm-MULTIBONE injection

Table of the components

<table>
<thead>
<tr>
<th>Name of the components</th>
<th>Quantity per volume unit</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>153Sm-EDTMP</td>
<td>2500 MBq</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2 Radiation physical properties of 153Sm isotope

Physical half-life: 47.26 hours

Energy and intensity of the emitted

<table>
<thead>
<tr>
<th>Gamma particle</th>
<th>Energy (keV)</th>
<th>Intensity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>133 keV</td>
<td>100</td>
<td>90.5</td>
</tr>
<tr>
<td>120 keV</td>
<td>10</td>
<td>8.7</td>
</tr>
<tr>
<td>96 keV</td>
<td>10</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Gamma energy of the emitted 153Sm isotope is in the range of 10 keV to 133 keV. By-product radionuclides are not produced.

2.4 Interaction with other medicinal products and other forms of interaction

None stated.

2.5 Pregnancy and lactation, paediatrics

Pregnancy and lactation

Administration of the product to pregnant or lactating women is contraindicated unless the required therapeutic benefit to the patient outweighs the potential risk to the foetus. Pregnancy testing before administration is highly recommended. Due to the increased accumulation of the 153Sm radioactivity in the bone lesions a selective, local radionuclide therapy can be carried out.

4.3 Pharmacokinetics

153Sm-samarium chloride precursor can be used in case of administration of double dose of the preparation.  153Sm-Multibone can be used in case of administration of double dose of the preparation.

5.2 Pharmacokinetic properties

Intravenously administered 153Sm-EDTMP leaves the bloodstream rapidly; 80-90% of the injected dose is excreted within half an hour and 98% after 4 hours. The excretion can be characterised with two parallel processes described with T1/2 values as follows:

Quick phase: T1/2 = 14 min

Slow phase: T1/2 = 11.5 hours

The activity necessary to achieve the therapeutic effect appears in the bone lesions 1-2 hours after administration. During that time 47-77% of the injected radioactivity is localized in the bone lesions, in case of more extensive lesions the accumulation is greater. The non-bound activity appears in the kidneys and the urinary bladder (70-90% of the injected dose, 90% after hours and 100% after 12 hours). A negligible amount qualifies in the liver and the intestines.

5.3 Preclinical safety data

Intravenous acute toxicity experiments on mice showed that no clinical symptoms can be observed up to 250 mg/kg of bodyweight. Labelling of the MULTIBONE kit with 153Sm-samarium chloride precursor is easy and safe.

The injection prepared by using one vial of MULTIBONE kit and one vial of 153Sm-samarium chloride precursor represents the dose of one patient. The amount of 153Sm-EDTMP in 1 MBq of 153Sm-Multibone does not have effect on the radiochemical purity of the product; the quantity per volume unit

Table of excipients

<table>
<thead>
<tr>
<th>Name of the components</th>
<th>Quantity per volume unit</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipient</td>
<td>Water for injection</td>
<td>1 ml</td>
</tr>
</tbody>
</table>

6.1 List of precautions

Stimulates the olfactory, gustatory, acidosis, guaivestin sodium, chloride, sodium for Injection.

6.2 Incompatibilities

Multibone is incompatible with any alkaline media of greater quantity than the buffer capacity of the product since it increases the pH value above 8. Furthermore, when used with a buffer capacity of greater than 20 meq/l, the pH value should be adjusted to pH 7.4 by the addition of 10 ml/l of 1.4 M sodium hydroxide and 10 ml/l of 1.4 M hydrochloric acid. Consequently, the cap and the stopper of the vial can be only removed right before use of the injection. Labelling the MULTIBONE kit with 153Sm-samarium chloride precursor for labelling is incompatible with several more media because it would cause hydrolysis of the product. In case of intravenous administration of 153Sm-EDTMP to a patient the bone lesions are excreted via the urine, excretion via the bowel system is negligible. The beta particles of 110 keV energy emitted by 153Sm radinucleide, which are not ionizing in 10 cm of tissue, cause a minimum dose to the patient by the decay of the tissue.

The quantity of radiation energy that is absorbed per unit mass of tissue is described with T1/2, the mean time required for the absorbed dose to decrease by 50%.

Quantity per volume unit

T1/2 = 11.5 hours

As with all radiopharmaceuticals, the radiation energy is transmitted from the radioactive isotope to the patient by the decay of the tissue.

The neutron flux of the reactor is: \( 5 \times 10^{12} \text{ neutron.cm}^{-2} \text{sec}^{-1} \) at the reactor exit. By-product radionuclides are not produced.

The neutron flux of the reactor is: \( 5 \times 10^{12} \pm 2 \times 10^{12} \text{ neutron.cm}^{-2} \text{sec}^{-1} \) at the reactor exit. By-product radionuclides are not produced.
6.6.1 Control of the drug product

6.6.1.1 Principle

Radiochromatic purity of $^{153}$Sm-EDTMP is tested by using paper chromatography.

6.6.1.2 Method

Stationary phase

3 pieces of 1.5 x 20 cm Whatman ET-31 (catalogue code: 3031015)

Mobile phase

Phosphate buffer, pH=7.5

Temperature

Room temperature (20–25ºC)

Test solution

The solution in the vial

Distribution of radioactivity

$^{153}$Sm-EDTMP injection

$^{153}$Sm-samarium chloride R = 0.0–0.1

$^{153}$Sm-EDTMP R = 0.0-0.1

6.6.1.3 Text

Use 3 pieces of 1.5 x 20 cm ET-31 paper strips. Apply to the strips 5 – 5 µl (equal volume) of 0.5 mmol/L solution to be tested at 1.5 cm from the end of the paper. Develop the strips over a 12 - 15 cm path in phosphate buffer (pH 7.5).

Dry the strips, impregnate them with 5% polystyrene solution, and allow them to dry again. Determine the radiochromaticity by using a scanner. Radiochromatic purity is calculated by using the ratio of strip areas.

The activity corresponding to $^{153}$Sm-EDTMP peak compared to the total radioactivity on the strip as 100% provides the radiochemical purity, which should be not less than 95% at expiry.

6.6.2 Handling of radioactive waste

The remainder of the solution and strips should be stored as radioactive waste according to the regulations for radioactivity.

7 Marketing Authorization holder

7.1 Enstatele of Isotope Co., Ltd.

1121 Budapest, Körössy Tégla str. 29-33.

Telephone: 36 1 392 2577; 995 9081

Fax: 36 1 392 2575

E-mail: commerce@enstco.hu

Home page: www.enstco-int.com

8 Marketing Authorization Number

2007/3276/EE/EN (valid until 11/2012)

9 Date of first authorisation / Renewal of the authorisation


b.) First authorisation: 07.08.1997.

10 Date of revision of the text


11 Authorisation number of the original Hungarian SmPC: 484/40/04

This SmPC was translated by the manufacturer based on the original Hungarian document.

12 Possible side effects

• Possible side effects

• Storing SAMARIA-MULTIBONE INJECTION

SAMARIA-MULTIBONE INJECTION, which is an injectable solution for intravenous use, contains $^{153}$Sm-samarium radioactive. Active ingredient of this medicinal product—$^{153}$Sm-samarium

Other ingredients: stannous chloride dihydrate, ascorbic acid, anhydrous glucose, hydrogen chloride and water for injection.

Marketing Authorisation Holder of SAMARIA-MULTIBONE INJECTION:

Institute of Isotopes Ltd.

H-1121 Budapest, Körössy Tégla str. 29-33. Hungary

13 In case of overdose

What to do in case of overdose?

Use of SAMARIA-MULTIBONE INJECTION is strictly contraindicated, thus the probability of overdose is low. In the unlikely event of overdose, it was proven by experiments that the excess of the injection has no damaging effects.

There are strict rules and regulations referring to the handling, shipping and storage of radioactive material. SAMARIA-MULTIBONE INJECTION can only be used designated clinical settings or institutions. Only properly trained, specialise staff can handle, use and annihilate this injection and are properly trained to manage radioactive materials can deal with this medicament. These people instruct you about the precautions and warnings. Comply with their instructions.

14 Possible side effects of SAMARIA-MULTIBONE INJECTION

Appearance of side effects and undesirable symptoms to be felt are not expected. Your blood parameters can temporarily worsen but it can be controlled by your doctor.

If you notice any side effects, PLEASE INFORM YOUR DOCTOR.

15 Storing SAMARIA-MULTIBONE INJECTION

Staff of the hospital is responsible for the storage of the product and for avoidance of administering expired product.

Keep out of the reach of sight and children of people who are not authorised to handle, use or transport this product.

Store at room temperature at 15 – 25ºC, in its original container. Storage conditions and expiry date is indicated on the label of the vial containing the medicament.

This leaflet was prepared on 30.05.2003.

Additional information

The information given above is a brief summary. For further information about SAMARIA-MULTIBONE INJECTION ask your doctor.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder (Institute of Isotopes Co. Ltd.)

Authorisation number of this leaflet: 464/40/04

Marketing authorization number: OGYT-T-1982/01

This leaflet was translated by the manufacturer based on the original Hungarian document.