SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

^{153}Sm-Multibone kit for radiopharmaceutical preparation and ^{153}Sm-chloride radioactive precursor

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition of Multibone powder for injection

Component	*Quantity per vial*	*Function*
Active substance		
Ethylene-diamine-tetramethylen-phosphonate (EDTMP)	25.0 mg	Organ-specific chelating agent of ^{153}Sm radioisotope

Composition of ^{153}Sm-chloride radioactive precursor

Name of the components	*Quantity per volume unit*	*Function*
Active ingredient		
[^{153}Sm]samarium chloride	2500 MBq	Radionuclide providing radiation therapeutic effect

Composition of ^{153}Sm-radioactive injection

Component	*Quantity per vial*	*Function*
Active substance		
^{153}Sm- EDTMP	2500 MBq	Local, lesion-specific radiation therapeutic effect

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

^{153}Sm-Multibone injection can be prepared in situ at the site of the use ie. at isotope laboratories of clinics or hospitals by mixing Multibone powder for injection (lyophilisate in the vial), physiological saline solution and ^{153}Sm-samarium chloride radioactive precursor.

Pharmaceutical form of Multibone kit: powder for injection
Pharmaceutical form of ^{153}Sm-samarium chloride: radioactive precursor. **It must not be administered directly to the patient, it serves only for labelling of Multibone kit.**
Pharmaceutical form of ^{153}Sm-Multibone: injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INDICATION FIELD: ISOTOPE THERAPY
Palliative, analgesic treatment of previously localised bone metastases. Use of the preparation highly recommended in the 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 some other tumours

4.2 Posology and method of administration

Administration of ^{153}Sm-Multibone injection for children under 18 years of age is contraindicated except if the therapeutic effect outweighs the risk associated with the radiation exposure.

Posology
Labelling should be performed by using 2500 MBq of ^{153}Sm precursor. The individual patient dose is 2500 MBq of ^{153}Sm-Multibone per 70 kg bodyweight.

Method of administration
^{153}Sm-Multibone should be administered slowly, intravenously to the patient. After this, the patient should drink 100 mg/10 kg of bodyweight of liquid and/or the blood circulation should be stimulated by intravenous administration of 20 ml of physiological saline solution. Medical attention should be provided for the patient's benefit for several hours.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy and lactation
- Under 18 years of age (See section 4.2) except if the therapeutic effect outweighs the risk associated with the radiation exposure
- Chemotherapy or external irradiation in the six week prior therapy
- If the patient got bisphosphonates in the two weeks prior therapy
- in case of patient with seriously impaired bone marrow, since the risk of the therapy will be higher than the advantageous effect expected. The contraindication is especially valid if the following quantitative parameters of the patient are out of the limits given below:
  -White cell count $< 3 \times 10^9$
  -Platelet count $< 120 \times 10^9$
  -Serum creatinine > 120 µmol / litre
  -Karnofsky index ≤ 60 %
- if the patient does not provide an oral or written consent of being treated with the radionuclide.

4.4 Special warnings and precautions for use

^{153}Sm-Multibone injection contains radioactive isotope. Radioactive medicinal products should be received, used and administered only by authorised person in designated clinical settings. Receipt, storage, use, transfer and disposal of the radioactive medicinal products are subject to the regulations and appropriate licences of the competent authorities.
Way of handling of radiopharmaceuticals should meet the criteria both of radiation safety and pharmaceutical quality requirements. Appropriate lead shieldings should be used during the preparation and the examination, to protect the patient and the staff from the risk of the radiation, as it is possible.
^{153}Sm-Multibone therapy can be carried out in case of outpatients. After administration of the preparation the patient should be kept under medical attendance for several hours because the activity not bounded to the bone lesions is excreted during this period. It is advantageous that the physical half life of ^{153}Sm is 47 hours, after ten fold of the half life (3 weeks) the radioactivity can be considered decayed.

4.5 Interaction with other medicinal products and other forms of interaction

^{153}Sm-Multibone therapy must not be applied concurrently with chemotherapy and external irradiation.
Other bisphosphonates must be withheld 2 weeks prior therapy.

4.6 Pregnancy and lactation

Pregnancy
Exposure to ionising radiation during pregnancy is a potential for development of hereditary defects, therefore use of ^{153}Sm-Multibone is contraindicated in case of pregnancy.
When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed pregnant until proven otherwise. Alternative techniques which do not involve ionising radiation should be considered.
Lactation
Use of ^{153}Sm-Multibone is absolutely contraindicated during lactation.
There are no detailed data relating to the excretion of ^{153}Sm-Multibone in breast milk, therefore the treatment would pose a risk to the child.

4.7 Effects on ability to drive and use machines

The medicine does not influence directly the ability to drive and use machines.
In occurrence of unexpected adverse reactions driving and/or working with machines should be reconsidered.

4.8 Undesirable effects

The reporting rate of adverse reactions is classified as very common (>1/10), common (>1/100-<1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1,000), very rare (<1/10000, including individual cases).

Gastrointestinal disorders	
common	nausea
Musculoskeletal and connective tissue disorders	
common	Transient increase of bone pain
General disorders and administration site conditions	
Very rare	Tissue necrosis
Blood and lymphatic system disorders	
Very common	Transient myelosuppression

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. However these effects are hardly expected regarding the applied amount of activity.

4.9 Overdose

^{153}Sm-Multibone should be used and administered only by authorised persons in designated clinical setting. The risks to be expected are associated with administration of excess radioactivity.
No case of overdose has been reported.
In case of incidental overdose be ready to provide life support.
Radiation dose to the body can be reduced by increased and frequent diuresis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: different radiopharmaceuticals for pain palliation ATC code: V10B X 02
Active ingredient of ^{153}Sm-MULTIBONE is ^{153}Sm-EDTMP, which rapidly leaves the bloodstream and accumulates mainly in the bone lesions, since the blood supply of the bone and the bone building (osteoblast) activity are increased in the bone lesions. Healthy bone accumulates less quantity and the accumulation by soft tissues is negligible. The mechanism of the uptake by the bone is precipitation and chemisorption in the inorganic matrix of the bone (hydroxy-apatite of ionic nature, $Ca_{10}(PO_4)_6(OH)_2$). Due to the increased accumulation of the ^{153}Sm radioactivity in the bone lesions a selective, local radionuclide therapy can be carried out. 47-77 % of the administered 2500 MBq of ^{153}Sm-EDTMP appears in the bone and bone lesions. The bone lesion / normal bone activity ratio can be even 16:1. More and extensive lesions accumulates more ^{153}Sm-EDTMP.
^{153}Sm-Multibone not bound by the bone tissues is excreted via the urine; excretion via the hepatobiliary system is negligible.
The beta particles of 705 keV energy emitted by ^{153}Sm radionuclide, which are absorbed in bone metastases within 0.6 mm average distance, provide the therapeutic effect of ^{153}Sm-Multibone. The upper limit of the absorption range is 3 mm. The beta particles transmit their full energy to the tissues, bone lesions, in which they are absorbed. This energy transfer causes the palliative effect by the destruction of the tissues.
The quantity of radiation energy absorbed per unit mass of tissue is the absorbed dose, of which effective range is 5 – 50 Gy. This range can be achieved by administering 2500 MBq of ^{153}Sm-Multibone per patient. This amount of radioactivity cause myelosuppresion 1 – 2 weeks after administration which normalises in 3 – 4 weeks if the administered activity of ^{153}Sm is not higher than 40 MBq/kg of bodyweight.

5.2 Pharmacokinetic properties

Intravenously administered ^{153}Sm-EDTMP leaves the bloodstream rapidly; 88-90% of the activity is eliminated within half an hour and 98% within 4 hours. The excretion can be characterised with two parallel processes described with $T_{1/2}$ values as follows:
Quick phase $T_{1/2} = 14$ min, Slow phase $T_{1/2} = 11.5$ 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 localised in the bone and bone lesions, in case of more lesions and more extensive lesions the accumulation is greater.
The non-bound activity appears in the kidneys and the urinary bladder (70% 2 hours after being injected, 90% after 4 hours and 100% after 12 hours). A negligible quantity appears in the liver and the intestines.

5.3 Preclinical safety data

Intravenous acute toxicity experiments on mice showed no clinical symptoms up to 50 mg/kg of bodyweight. Labelling of the Multibone kit with [^{153}Sm]samarium chloride precursor is easy and safe.
The injection prepared by using content of one vial of Multibone kit and one vial of [^{153}Sm]samarium chloride precursor represents the dose of one patient. The administered amount of ^{153}Sm-EDTMP in case of an average 70 kg bodyweight is equivalent to 0.357 mg EDTMP per kg of body weight, which is equal to 0.72 % of the no observed effect level. Thus, the use of the product considered safe. Further advantage of the product is that the effective radioactivity in the recommended 2500 MBq ^{153}Sm activity does not have effect on the radiochemical purity of the product; the quantity of the radiochemical impurities does not exceed 5%. As a result, the kit considered safe from the labelling point of view.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sm-Multibone powder for injection

Component	*Quantity per vial*	*Function*
Excipients		
Stannous chloride dihydrate	1.0 mg	Promoter of complexation of ^{153}Sm at room temperature
Ascorbic acid	5.0 mg	Stabiliser
Glucose, anhydrous	10.0 mg	Filler

^{153}Sm-chloride radioactive precursor

Name of the components	Quantity per volume unit	Function
Excipients		
Sodium chloride	9 mg	Ionic strength adjustment to avoid hydrolysis of ^{153}Sm
Water for injection	1 ml	Solvent

6.2 Incompatibilities

For preparation of ^{153}Sm Multibone injection only ^{153}Sm samarium chloride radioactive precursor can be used.

6.3 Shelf life

Multibone powder for injection (lyophilised non-radioactive components in glass vial closed with ruber stopper and aluminium kombicap): 12 month from production
^{153}Sm samarium chloride radioactive precursor: 5 days from production (indicated on the labels of the glass vial, the lead container and the tin box)
^{153}Sm Multibone injection: should be used in 24 hours after labelling

6.4 Special precautions for storage

Multibone powder for injection: Store in refrigerator (2 - 8°C) in its original packaging.
^{153}Sm samarium chloride radioactive precursor: Store below 25°C.
^{153}Sm Multibone injection (Sm- Multibone labelled with ^{153}Sm isotope, ^{153}Sm-EDTMP injection): must not be stored above 25°C.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.
For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Multibone powder for injection
The injection vials of Multibone kit contain the sterile, pyrogen-free and freeze-dried components. The labelled 6 ml injection vials (Type I) are closed with rubber stopper and tear-off kombicap (aluminium commbined with polypropylen). One box contains six vials.

^{153}Sm samarium chloride radioactive precursor
The 6 ml glass vial (Type I) containing the ^{153}Sm samarium chloride radioactive precursor is closed with rubber stopper and tear-off aluminium cap. The labelled vial is placed in a lead container. The lead container is packed in a labelled tear-off metal can.
One vial contains 2500 MBq sterile ^{153}Sm samarium chloride radioactive precursor solution.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Multibone kit can only be administered to patient after labelling with ^{153}Sm samarium chloride radioactive precursor. Never administer ^{153}Sm samarium chloride radioactive precursor or Multibone kit without performing the labelling.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

OGYI-T-9192/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 August 1997

10. DATE OF REVISION OF THE TEXT

01 October 2014

This SPC was translated by the manufacturer based on the original Hungarian document, authorized by the Hungarian National Institute of Pharmacy on 21.12.2009 and revised on 01. 10. 2014

11. DOSIMETRY

A single dose of a patient in case of 70 kg average body weight contains 2500 MBq of ^{153}Sm activity. 1 MBq of the injection induces the following absorbed doses in the listed organs:

Organ	Absorbed dose [mGy/MBq]
Trabecular bone	2.32
Cortical bone	0.86
Red bone marrow	1.86
Kidneys	0.134
Urinary bladder	0.120
Stomach	0.026
Liver	0.043

Radiation physical properties of ^{153}Sm isotope

Physical half life:	46.27 hours	
Energy and intensity of the emitted	69 keV	4.85 %
gamma particles:	103 keV	29.8 %
	635 keV	32.2 %
Energy and intensity of the emitted beta	705 keV	17.5 %
particles:	808 keV	49.6 %

^{153}Sm isotope is manufactured in nuclear reactor by neutron irradiation according to the reaction given below:^{152}Sm(n,γ)^{153}Sm. By-product radioisotopes are not produced.
Specific activity: > 5 GBq/mg. Activity concentration: 2500 MBq/ml
Radionuclidic purity at the time of utilisation: > 99.9%
Radiochemical purity: > 95 %
During the decay stable ^{153}Eu is produced.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Remove the protective foil and lift the upper part of the paper box up to access the vials. During the use of this product the rules and regulations referring to the radioactive materials should be observed.
[^{153}Sm]samarium chloride precursor is a radioactive product supplied in Type A packaging. To open the packaging, follow the instruction given below.
Tear the top panel of the metal can off. Remove the upper part of the plastic foam insert. Take the lead container out of the metal can and put it on the working area. Remove the seal strip and then the upper part of the lead container. This way the glass vial containing the radioactive material is readily accessible. Comply with the regulations for radiation safety.
Multibone kit can only be administered to patient after labelling with ^{153}Sm samarium chloride radioactive precursor. Never administer ^{153}Sm samarium chloride radioactive precursor or Multibone kit without performing the labelling.
^{153}Sm-Multibone injection contains radioactive isotope. For handling, shipping and storage of this product the rules and regulations referring to the radioactive materials should be observed.

Labelling procedure

Place the glass vial containing the freeze-dried material in a small lead container of 15 mm wall thickness (type KT-3). Under aseptic conditions inject 2.0 ml of physiological saline solution into the vial via the rubber stopper by using a sterile syringe. After complete dissolution of the powder, inject the total amount of [^{153}Sm]samarium chloride precursor (activity: 2500 MBq, volume: 1 ml) with a sterile syringe equipped with lead shielding into the vial containing the previously prepared EDTMP solution via the rubber stopper. Shake the vial thoroughly and allow it to stand at room temperature for 15 minutes. The total amount of ^{153}Sm-Multibone injection can be intravenously administered to the 70 kg patient. pH of the injection is in the range of pH = 5.0-8.0 . The labelled preparation must be used in 24 hours after labelling. The quantity of the radiochemical impurities must not exceed 5% during that time.

Control of the drug product

Radiochemical purity of ^{153}Sm-Multibone is tested by using paper chromatography.
Stationary phase: 3 pcs of 1.5 x 20 cm Whatmann ET-31 (catalogue code: 3031915)
Mobile phase: Phosphate buffer, pH=7.5
Temperature: Room temperature (20–25ºC)
Test solution: The solution in the vial
Distribution of radioactivity
^{153}Sm-samarium chloride Rf = 0–0.1, ^{153}Sm-EDTMP Rf = 0.9–1.0
Test: To one strip apply 5 µl of the 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 radioactivity by using a scanner. Radiochemical purity is calculated by using the data of three replicates.
Radiochemical purity is calculated by using the peak area data. The activity corresponding to ^{153}Sm-EDTMP peak compared to the total activity on the strip as 100% provides the radiochemical purity, which should not be less than 95% at expiry. Any unused product or waste material should be disposed of in accordance with local requirements.

IZOTOP

PACKAGE LEAFLET: INFORMATION FOR THE USER

^{153}Sm-Multibone kit for radiopharmaceutical preparation and ^{153}Sm-chloride radioactive precursor

Ethylene-diamine-tetramethylen-phosphonate,
^{153}Sm samarium chloride

Read all of this leaflet carefully before this medicine is used for your examination.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT Sm-MULTIBONE IS AND WHAT IT IS USED FOR

^{153}Sm-Multibone injection is a radiopharmaceutical preparation which can be used for palliation of pain caused by bone metastases of breast cancer, prostate cancer and other types of cancer.
After intravenous administration, ^{153}Sm-Multibone is transported to the bones via the blood circulation. It accumulates in the bones and binds to the pain causing harmful tissues. Due to the radioactive isotope content these tissues are exposed to continuous radioactive radiation. This radiation damages the tissues palliating this way the pain.
This medicinal product is for therapeutic use only.

2. BEFORE YOU USE Sm-MULTIBONE

Do not use Sm-Multibone

- if you are allergic (hypersensitive) to the active substance or any of the other ingredients of Sm-Multibone.
- If you are pregnant or breast feeding
- If you are under 18 years of age, except if the therapeutic effect outweighs the risk originating from the radiation
- Chemotherapy or external irradiation in the six week prior therapy
- If the patient got bisphosphonates in the two weeks prior therapy
- in case of patient with seriously impaired bone marrow, since the risk of the therapy will be higher than the advantageous effect expected. The contraindication is especially valid if the following quantitative parameters of the patient are out of the limits given below:
  - White cell count $< 3 \times 10^9$
  - Platelet count $< 120 \times 10^9$
  - Serum creatinine > 120 µM / litre
  - Karnofsky index ≤ 60 %
- if you do not provide an oral or written consent of being treated with the radionuclide.

Make sure you carry out the doctor's instructions both before and after the examination in order to avoid radioactive exposure of other people and the radioactive contamination of the environment.
The non-bounded proportion of the radioactive isotope is excreted in the urine. Flush your urine with abundant quantity of water two or three times and wash your hands thoroughly. Be careful not to drop urine drips to other places than the WC. Change your underwear if it becomes contaminated and wash it separately by using abundant quantities of water.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
^{153}Sm-Multibone therapy must not be applied concurrently with chemotherapy and external irradiation.
Other bisphosphonates must be withheld 2 weeks prior therapy.
You can continue your usual analgesics. If the pain reduces or ceases, consult with your doctor about the discontinuation of the analgesics.

Using Sm-Multibone with food and drink

You can take any food or drink.

Pregnancy and breast-feeding

It is important to tell your doctor if there is any possibility that you are pregnant or if you breast-feeding.
^{153}Sm-Multibone must not be used if you are pregnant or breast-feeding.

Driving and using machines

You can drive and use machines, but be careful. Do not ride on a bicycle. Keep away from situations in which you can have a fall or can be injured. In occurrence of unexpected adverse reactions driving and/or working with machines should be reconsidered.

Important information about some of the ingredients of Sm-Multibone

^{153}Sm-Multibone injection contains radioactive isotope; after its administration you are exposed to radiation.
Receipt, storage, use, transfer and disposal of the radioactive medicinal products are subject to the regulations and appropriate licences of the competent authorities. Radioactive medicinal products should be received, used and administered only by authorised person in designated clinical settings
These people give you instructions about the precautions and warnings. Comply with their instructions.

3. HOW TO USE Sm-MULTIBONE

^{153}Sm-Multibone injection is administered intravenously.
Amount of the administered activity is decided by your doctor according to the prescriptions and your state of health.

What should you do if you received overdose of the medicinal product?

Since ^{153}Sm-Multibone injection is given by a doctor under controlled conditions, the probability of overdose is low. In the unlikely event of overdose, excess of the injection has no damaging effects accordint to the experiments.

4. POSSIBLE SIDE EFFECTS

Like every medicinal product, ^{153}Sm-Multibone injection might cause adverse reactions, but such effects do not appear in every case.
Classification of side effects:
Very common: More than one of ten treated patient
Common: One to ten case of hundred treated patient
Very rare: Less than one case of ten thousand treated patient
The known side effects are the follows:
Nausea (common), transient increase of bone pain (common), tissue necrosis (very rare), Transient myelosuppression (very common)

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. However these effects are hardly expected regarding the applied amount of activity
If any adverse reaction becomes serious, inform your doctor.

5. HOW TO STORE Sm-MULTIBONE

Keep out of the reach and sight of children and people who are not authorized to handle, use or transport this product!
Hospital staff will ensure that the product is stored correctly and not used after expiry date stated on the label.
Sm-Multibone powder for injection: should be store in refrigerator at 2-8 °C in its original packaging.
^{153}Sm-samarium chloride radioactive precursor: is to be stored below 25°C, considering the regulations for radiation safety.
^{153}Sm-Multibone injection: is to be stored below 25°C, and must be used within the 24 hours after labelling.

6. FURTHER INFORMATION

What Sm-Multibone contains
- Active substance of Sm-Multibone powder for injection: ethylene-diamine-tetramethylene-phosphonate (EDTMP)
- Active substance of ^{153}Sm samarium chloride radioactive precursor: ^{153}Sm samarium chloride
- The active substance of ^{153}Sm-Multibone injection: ^{153}Sm-EDTMP
- Other ingredients are: Stannous chloride dihydrate, Ascorbic acid, anhydrous glucose, sodium chloride, water for injection

What Sm-Multibone looks like and contents of the pack

^{153}Sm-Multibone injection is a colourless sterile solution which prepared at the site of the use ie. at isotope laboratories of clinics or hospitals by mixing Multibone powder for injection, physiological saline solution and ^{153}Sm samarium chloride radioactive precursor.
Packaging:
Sm-Multibone kit: 6 injection vial (containing the powder) in one paper box
^{153}Sm samarium chloride radioactive precursor: 1 injection vial containing the radioactive precursor in lead container and tin box

Marketing Authorisation Holder and Manufacturer

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