IZOTOP
INSTITUTE OF ISOTOPES CO. LTD.

... to make life painless

MULTIBONE

IN VIVO KIT
FOR 'ON THE SPOT' PREPARATION OF

^{153}SM-EDTMP INJECTION

Composition of the MULTIBONE kit (Sm-IK-26)

Active ingredient:	
Ethylenediamine tetramethylene phosphonate (EDTMP)	25.0 mg
Excipients	
Stannous chloride dihydrate	1.0 mg
Ascorbic acid	5.0 mg
Glucose, anhydrous	10.0 mg

Composition of the radioactive precursor (Sm-RA-26)

Active ingredient	
[^{153}Sm]samarium chloride	2500 MBq
Excipients	
Sodium chloride	9.0 mg
Water for injection	1.0 ml

Composition of the 'on the spot' prepared injection

^{153}Sm-MULTIBONE (EDTMP)	2500 MBq in 3.0 ml volume

Radiation properties

Physical half life of ^{153}Sm:	46.27 hours	
Energy and intensity of the emitted gamma particles	69 keV 103 keV 635 keV	4.85 % 29.8 % 32.2 %
Energy and intensity of the emitted beta particles	705 keV 808 keV	17.5 % 49.6 %
Specific activity	≥ 5 GBq/mg	
Radionuclidic purity	> 99.9 %	
Radiochemical purity	limit: ≥ 95 %	usual values obtained in the range of 99 ±1 %

CLINICAL PARTICULARS

Indications

Palliative, analgesic treatment of previously localised bone metastases. Use of Multibone is highly recommended in the case of the bone metastases of breats or prostate cancer.

POSOLOGY

The labelling of one Multibone vial 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.

Following the administration, the patient should drink 100 ml/10 kg of bodyweight of liquid and/or the blood circulation should be stimulated by administration of 20 ml of saline intravenously. During several hours, medical attention should be provided for the patient's benefit.

Outpatient's treatment is possible.

CONTRAINDICATIONS

The use of the product is contraindicated at the age under 18 years, except when the necessity and importance of the therapy outweighs the risk coming from the radiation exposure.

White cell count	$< 3 \times 10^9$
Platelet count	$< 120 \times 10^9$
Serum creatinine	> 120 μM / litre
Karnofsky index	< 60 %

The use of the product is contraindicated in case of pregnant or breast-feeding women, or if the patient does not provide an oral or written consent of being treated with the radionuclide.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

^{153}Sm-Multibone therapy can be carried out also in case of outpatients. After administration of the preparation, the patient should be kept under medical attendance for several hours because the activity not bound to the bone lesions is excreted during this period.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

None stated.

PREGNANCY AND LACTATION, PAEDIATRICS

Administration of Multibone to pregnant or lactating women is contraindicated unless the necessity and importance of acquiring the information outweighs the risk coming from the radiation exposure.

The product can be administered to women of childbearing age after the possibility of pregnancy has been precluded. It is recommended to treat these women in the first 10 days after menstruation.

Multibone should not be administered to patients below 18 years of age, unless the necessity and importance of acquiring the information outweighs the risk coming from the radiation exposure.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MULTIBONE has no direct influence on these abilities.

UNDESIRABLE EFFECTS

Early effects

1 – 2 hours after the intravenous administration nausea may occur.

After 2 – 3 days, temporary increase of the bone pain may occur, lasting for maximum 1 week. This 'flare-up' usually predicts the chance of the good therapeutic effect.

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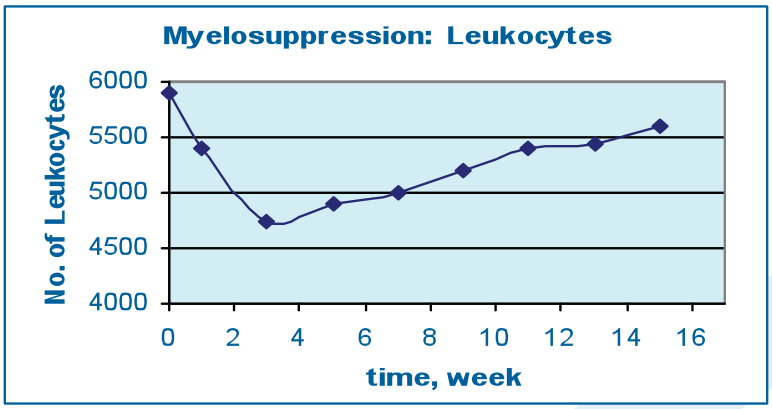
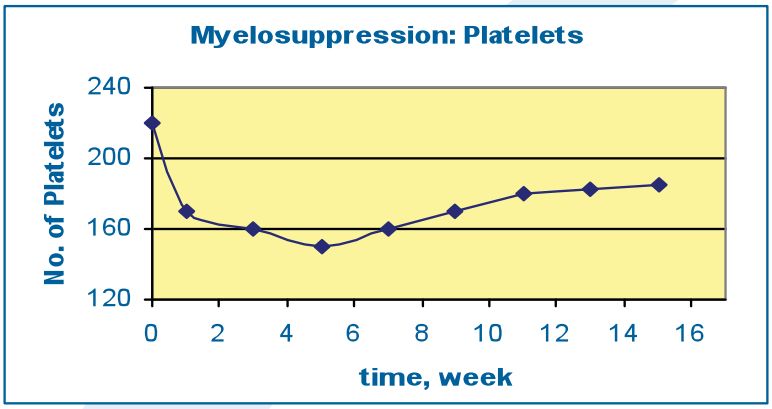




OVERDOSE

No case of overdose has been reported. In the unlikely event of overdose the vital functions of the patient should be supported.

RADIATION DOSIMETRY

A single dose of a patient contains 2500 MBq of ^{153}Sm activity.
In case of 70 kg body weight, 1 MBq of the injection causes the following absorbed doses:

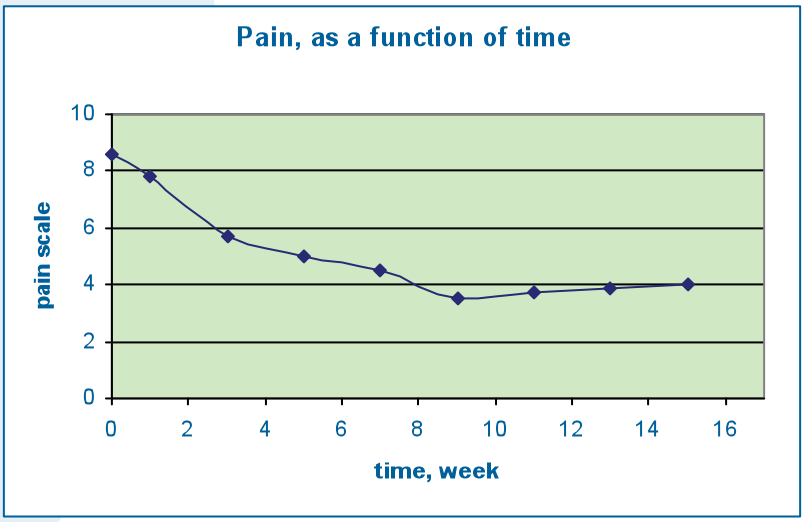
Organ	Absorbed dose [mGy/MBq]
Trabecular bone	2.32
Cortical bone	0.86
Red bone marrow	1.86
Kidneys	0.134
Urinary bladder	0.120
Stomach	0.026
Liver	0.043

PALLIATIVE EFFECT

Around 1000 patients have been treated with ^{153}Sm-Multibone injection.

The palliative effect usually lasts for 3 – 6 months. If necessary, the ^{153}Sm-Multibone treatment can be repeated after 3 months.

Pain relief has been quantified in case of 54 patients treated with ^{153}Sm-Multibone, by using a 10 grade pain scale. The lowest and highest score, i.e. 0 and 10 corresponded to the painless state and to the intolerable pain, respectively. Results are presented in the figure below:



PHARMACOLOGY

Pharmacodynamic properties

ATC code: V10B X 02

47-77% of the administered 2500 MBq of ^{153}Sm-EDTMP is accumulated in the bone and in the bone lesions. The lesion / normal bone activity ratio can be even 16:1. The non-bound activity of ^{153}Sm-Multibone is excreted almost exclusively via the urinary tract. The beta particles of average energy of 710 keV are absorbed in bone metastases around 0.6 mm distance as average, providing 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 of the lesions.

Pharmacokinetic properties

88-90% of the administered ^{153}Sm-Multibone activity is eliminated within half an hour and 98% of it within 4 hours. The excretion can be characterised by two parallel processes described by T1/2 values as follows:

Quick phase	T1/2 = 14 min
Slow phase	T1/2 = 11.5 hours

The activity needed 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, but in case of several 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.

Preclinical safety data

Intravenous acute toxicity experiments of Multibone on mice showed that no clinical symptoms have been observed up to 50 mg/kg of body weight. One patient dose (25 mg EDTMP in one vial labelled with 2500 MBq ^{153}Sm) corresponds to a value of 0.375 mg/kg body weight (in case of the average body weight of 70 kg) which is equal to 0.72 % of the dose causing absolutely no symptoms. Thus, MULTIBONE is considered as a safe product.

PHARMACEUTICAL PARTICULARS

List of excipients

Stannous chloride dihydrate, ascorbic acid, glucose anhydrous, sodium chloride, water for injection.

Shelf life

Shelf life of Multibone in vivo kit is 12 months from the day of production.

Shelf life of the ^{153}Sm precursor is 5 days from the day of the production.

The 'on the spot' prepared ^{153}Sm-Multibone injection should be used within 24 hours from labelling.

PACKAGING

One paper box of Multibone in vivo kit contains 6 vials of the sterile and bacterial endotoxin-free, freeze-dried, non-radioactive components. Vials are closed with rubber stopper and tear-off aluminium cap.

^{153}Sm-chloride precursor of activity of 2500 MBq, for preparation of a single dose of the ^{153}Sm-Multibone injection, is supplied in BEKA type 6 ml injection vials closed with rubber stopper and tear-off aluminium cap. The labelled vial is placed in a lead container, packed in a labelled tear-off metal can, containing plastic insert (Type A packaging for radioactive materials).

One vial from the six of Multibone kit in front of its paper box (left side), as well as the packaging of a single dose of the radioactive ^{153}Sm precursor (right side) are shown in the figure below.

SPECIAL PRECAUTIONS FOR STORAGE

Multibone in vivo kit should be stored at 2-8°C in its original paper box.

^{153}Sm-chloride precursor should be stored at room temperature in its original container.
One vial from the six of Multibone kit in front of its paper box (left side), as well as the packaging of a single dose of the radioactive ^{153}Sm precursor (right side) are shown in the figure below.

The 'on the spot' prepared ^{153}Sm-Multibone injection should be stored at room temperature in lead container fulfilling the rules concerning radioactive materials

LABELLING PROCEDURE

Place one vial of the Multibone in vivo kit in a small lead container of 15 mm wall thickness. Under aseptic conditions, inject 2.0 ml of physiological saline into the vial through the rubber stopper. After complete dissolution of the powder, inject the single dose (2500 MBq) of ^{153}Sm-samarium chloride precursor. Shake the vessel thoroughly and allow it to stand at room temperature for 15 minutes. After that, the ^{153}Sm-Multibone injection is ready for intravenous administration.

CONTROL OF THE RADIOCHEMICAL PURITY

Radiochemical purity of ^{153}Sm-Multibone is tested by using paper chromatography

Stationary phase: 1.5 x 20 cm stripes of Whatmann ET-31 (catalogue code: 3031915)
Mobile phase: Phosphate buffer, pH=7.5

Distribution of radioactivity: ^{153}Sm-chloride impurity at Rf = 0 – 0.1, ^{153}Sm-EDTMP at Rf = 0.9 – 1.0.

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

MANUFACTURER & MARKETING AUTHORIZATION HOLDER:

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