SUMMARY OF PRODUCT CHARACTERISTICS
(HEDP)

1. NAME OF THE MEDICINAL PRODUCT

PHOSPHOTECH (1-hydroxi-ethyliden-1,1-diphosphonicum- HEDP) in vivo kit for preparation of radiopharmaceutical product.

The pharmaceutical is to be prepared on the location of use (hospital or clinical laboratory) by mixing the content of the product and ^{99m}Tc-pertechnate eluate gained from any licensed ^{99}Mo/^{99m}Tc isotope generator.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

a.) Composition of PHOSPHOTECH in vivo kit:

Denomination of the components	Quantity per vial	Function
Active ingredient		
Potassium and sodium 1-hydroxi-ethyliden-1,1-diphosphonicum (HEDP)	9,0 - 14,5 mg	Organ -specific ligand of ^{99m}Tc radionuclide

b.) Composition of ^{99m}Tc-PHOSPHOTECH radioactive injection:

Denomination of the components	Quantity per vial	Function
Active ingredient		
^{99m}Tc -HEDP	1.0-3.7 GBq	Provider of organ-specific diagnostic information

3. PHARMACEUTICAL FORM

Pharmaceutical form of PHOSPHOTECH in vivo kit: Powder for injection
Pharmaceutical form of ^{99m}Tc-HEDP: Radioactive, sterile injection

CLINICAL PARTICULARS
This medical product is for DIAGNOSTIC purposes only.

Field of indication: bone scintigraphy, especially recommended in the following cases:
- Primer bone tumors
- Bone metastases of other tumors (e.g. prostate, breast, lung cancers)
- Osteomyelitis
- Metabolic bone diseases
- Paget's disease

4. PHARMACOLOGICAL PROPERTIES

After administered intravenously the labelled ^{99m}Tc-HEDP (1-hydroxi-ethyliden-1,1-diphosphonicum) leaves the blood and concentrates mainly in the skeleton and to an almost

negligible extent in the soft tissues. The mechanism of the uptake is ion exchange and chemisorption in the inorganic matrix of the bone: hydroxy-apatite [Ca10(PO4)6(OH)2], which is of ionic nature. Phosphate groups on the surface of the bone matrix take part in an ion exchange reaction with the free -PO3H2 groups of HEDP coordinated to technetium. This way radioactive ^{99m}Tc binds on the bone matrix. This process is accomplished with normal bone as well but binding is significantly more extensive where

- the blood supply of the bone is increased,
- the bone formation activity (osteoblast function) is increased.

Therefore, on the location of bone lesions (primer tumours, metastases, splittings and fractions of the bone, inflamed bone) intensive radioactivity is observed, which enables excellent imaging.

A much smaller quantity of injected ^{99m}Tc-HEDP binds to the blood plasma proteins, which results in slower excretion and a very slight body background. ^{99m}Tc-HEDP not bound to the skeleton washes out from the body in the urine. Washout through the hepatobiliary system is usually negligible.

58% of ^{99m}Tc-HEDP injected into rats localises in the femur in the 3rd hour after administration and only 10% is excreted until the 48th hour. As of experiments on beagles 30-36% of the introduced dose is collected in the bone and its 64% is excreted through the kidneys. The cumulated ratio in the urine of dogs is 78.3%.

In human experiments 20-24% of ^{99m}Tc-HEDP is bound in the skeleton, the ration of the bone and the soft tissue background is 5:1, while the bone metastasis / normal bone ratio varies between 1.4:1 and 5.3:1, consequently, the bone metastases appear in the bone scintigram as conspicuous activity excesses. The same applies to fractures, inflammations and the cases of osteoporosis and hyper-parathyroidism.

5. Pharmacokinetic properties

^{99m}Tc-PHOSPHOTECH introduced intravenously leaves the bloodstream in three parallel processes described with exponential curves:

- 79% of the activity T1/2 = 3.8 min
- 17.2% of the activity T1/2 = 51.6 min
- 3.8% of the activity T1/2 = 10.2 hours

In the quickest (3.8 min) phase can ^{99m}Tc-PHOSPHOTECH is excreted to the extravascular space, the medium phase corresponds to the bone uptake. Dissociation of plasma protein bound ^{99m}Tc-HEDP takes place during the slowest phase. Binding of ^{99m}Tc-HEDP to the red blood cells is negligible.

The maximum bone uptake of ^{99m}Tc-PHOSPHOTECH can be **observed 3-4 hours after administration** and remains unchanged for approximately 24 hours.

^{99m}Tc-HEDP is excreted with the urine. The maximum activity is present in the kidneys 30-60 minutes after being injected. In case of normal kidney function approximately 60-80% of the total amount is filtered out glomerularly (50% in 6 hours, 65% in 24 hours, 78% in 5 days). Activity appearing in the liver and the intestines is minimal.

5.1. Radiophysical properties of the radionuclide and the absorbed dose values

Physical half life	6 hours
Energy of the emitted gamma-photons	140 keV
Energy of the emitted beta-particles	none

A single dose of a patient contains 370-555 MBq activity. In case of 70 kg average weight 1 MBq of the injection induces the following absorbed dose in the listed organs:

Organ	Absorbed dose values mSv / MBq
Ovaries	0,004
urinary bladder	0,048
Kidneys	0,007
Red bone marrow	0,009
Skeleton	0,063
Testes	0,002

6. Instruction for use and handling

Preparations are prepared in a medical facility immediately before use by adding aseptic conditions into the vial of reagent 5 ml of eluate from the generator of technetium-99m, with volume activity 185-740 MBq/ml. If necessary, conduct previously dilution of the eluate with isotonic sodium chloride solution to the required volume activity.
Drug in 20 minutes ready for use after the complete dissolution of the reagent.
4.0-6.0 pH of the finished product.
Drug is injected 5 MBq/kg (0.15 mCi/kg). One vial can be used for the survey's five patients. Study conducted by means of gamma camera or a scanner, **3 hours after injection**, after emptying the bladder. Scintigram or skennogrammy estimate by the distribution of the drug in the skeleton. Area of bone lesions characterized hyperfixation drug.

CONTRAINDICATIONS

Specific contraindications are not known. Prior to examination, it is necessary to inquire possible pregnancy. Before the necessary examination of breast-feeding women, sucking nutrition should be converted to a substitute nutrition for 24 hours.

INTERACTIONS

At the doses used drug interactions were not observed.

WARNINGS

The radiopharmaceutical can be used by authorized person only. The preparation can not be used after expiry data given on package.

OVERDOSE

There is no information available about any actually occurred overdose. Should still such a case occur treatment should be directed towards the support of vital functions. Administration of higher activity than prescribed results in unnecessary absorbed radiation dose on the patient and her/his environment, which is to be avoided. However, should such an event occur as the result of an error or a mistake of the personnel first of all the actually injected activity value of ^{99m}Tc is to be determined. Then the absorbed dose (concerning both the whole body and the individual organs) is to be calculated based on the dosimetry table in paragraph 5.2. The table shows the absorbed dose values in mSv caused by introduction of 1 MBq ^{99m}Tc isotope, which is to be multiplied by the MBq value of the actually injected activity so that the required absorbed dose is obtained. Whether the patient should undergo a treatment and/or an administrative radiation safety procedure is to be decided according to the calculated values.

If administered as prescribed minimum 4.17 mg, maximum 8.33 mg of ^{99m}Tc-HEDP is introduced to the body. Pursuant to intravenous acute toxicity experiments on mice and cats no clinical symptoms can be observed up to 5 mg/kg body. In case as the result of an error or a mistake of the personnel the whole content of one vial is injected, it represents 14 mg. It equals to 0.36 mg/kg - calculated with an average body weight of 70 kg -, which is only 7.1% of the mentioned symptom free limit.
Consequently, no toxic effect is expectable in overdose.

Shelf life
1 years. After reconstitution: 5 hours. Do not store above 25°C after reconstitution.

Special precautions for storage
Store in a refrigerator (2°C-8°C). Keep the vials in the outer carton in order to protect from light.
For storage conditions after radiolabeling of the medicinal product, see section 6.3.
Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

Nature and contents of container
The labelled 10 ml injection vials are closed with rubber stopper and aluminum cap. One box contains six (6) vials, one Instruction Manual and one Quality Certificate.
After labeling with technetium-99m store in a suitable lead shield and use within 5 hours.
Do not use after the expiration date.