SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

^{99m}Tc-Tektrotyd, Kit for radiopharmaceutical preparation.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HYNIC-[D-Phe1, Tyr3-Octreotide] ·TFA, 16 µg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The kit for radiopharmaceutical preparation ^{99m}Tc-Tektrotyd is intended only for diagnostic examinations. ^{99m}Tc-Tektrotyd is[P01] a radiopharmaceutical intended for diagnostics of pathological lesions in which overexpression of somatostatin receptors occurs (especially subtype 2 and, to a lesser extent, subtypes 3 and 5) and which may be imaged with the use of labelled ligand.
These are especially:
- Gastro-entero-pancreatic neuroendocrine tumors (GEP-NET);
- pituitary adenomas;
- tumours originating in a sympathetic system; pheochromocytoma, paraganglioma, neuroblastoma, ganglioneurinoma and so on;
- medullary carcinoma of thyroid;
- the preparation may be potentially useful in the case of other tumours expressing somatostatin receptors of various intensity. Other tumours which may express overexpression of somatostatin receptors: breast cancer, malignant melanoma, lymphomas, prostate cancer, sarcoma, clear cell carcinoma of the kidney, differentiated carcinoma of thyroid, astrocytoma WHO I-IV (including glioblastoma multiforme G-M), meningioma, ovarian carcinoma.

4.2 Posology and method of administration

The preparation is intended for use in a hospital or specialist laboratories and departments of nuclear medicine by the personnel experienced in the use of radiopharmaceuticals.
^{99m}Tc-Tektrotyd is administered by single intravenous injection after labelling of the kit with a sterile, radicals free eluate solution from radionuclide generator 99Mo/^{99m}Tc according to the instruction concerning preparation of the drug for use and its disposal ï see section 12. For labelling of the kit, technet-99m may be used in the form of 1 ml sodium technetate (VII) [^{99m}Tc] (eluate with radionuclide generator 99Mo/^{99m}Tc) of activity of 740 MBq ï 1200 Mbq (to a maximum of 2200 Mbq). This amount is sufficient for examinations of 1 ï 2 adults.
Radioactivity of administered dose should be always adjusted regarding its diagnostic usefulness. In order to facilitate administration of the preparation, the solution of ^{99m}TcTektrotyd may be additionally diluted. Acquisition should be carried out in 2 ï 4 hours after intravenous administration of the preparation. The examination may be complemented by acquisition after 10 minutes, 1 hour and 24 hours after administration of a marker. It is recommended to carry out the examinations using Whole Body technique and SPECT[P02] of selected body parts.

Preparation of the patient for examination
Unless there are indications for other method of preparation of the patient, it is recommended to use light diet on the day before examination. On the day of examination, the patient should be fasted until the end of the first acquisition. If there is a need for conducting examination after 24 hours, the patient should be given a laxative in the evening preceding the examination. Method of preparation of the patient may depend on the used protocol of examination and localization of imaged lesions. However, optimal imaging of abdominal cavity is obtained after the use of liquid diet 2 days before the examination and after administration of laxatives on the day preceding the examination.

Dose of the preparation used in adults
The recommended activity for conducting one examination in an adult is within the limits of 370 to 925 MBq.

Elderly patients (above 65 years)
Literature data do not indicate the need for dosage adjustment.

Children
^{99m}Tc-Tektrotyd should not be used in patients aged below 18 years; there are no data concerning this age group

Use in patients with renal insufficiency
There is no need for dosage adjustment ï see section 4.4.

Repeated administration
^{99m}Tc-Tektrotyd is intended for a single intravenous administration. If there is a need for repeated administration, clinical indication and potential adverse events should be considered.

4.3 Contraindications

Hypersensitivity to HYNIC-[D-Phe1, Tyr3-Octreotide] or to any of the excipients or sodium technetate (VII) [99Tc]. Pregnancy.
In the case of breastfeeding, see section 4.6. In children and young persons, the dose should be possibly lowered.

4.4 Special warnings and precautions for use
The content of the vials of the kit for preparation of the radiopharmaceutical ^{99m}Tc-Tektrotyd is intended for use only after preparation of complex of ^{99m}Tc-Tektrotyd, solution for injections ï according to the instruction in section 12. The preparation should not be used before labelling.
Patients with renal insufficiency should be under special supervision ï renal excretion is prolonged, the patient is exposed to higher dose of radioactivity. Also, patients with liver failure should be provided with special care.
The radiopharmaceutical may be obtained, stored and administered to patients only by persons with special qualifications, in specialist clinics intended for this purpose. Obtaining, storage, therapeutic use, handling and disposal are subject to appropriate administrative regulations compliant with atomic law.
Radiopharmaceuticals intended for administration to patients should be prepared in appropriate way regarding radiological safety rules as well as pharmaceutical recipe.
^{99m}Tc-Tektrotyd should be prepared and used with exercising of caution so that personnel and patient exposure to radioactivity is lowered. There are no data on safety and efficacy of the use in children below 18 years of age.
Proper hydration of the patient in order to increase frequency of urination is needed in order to decrease dose of radioactivity to urinary bladder.
In the case of renal failure, exposure to radioactivity may increase. It should be taken into consideration while calculating dose of a radiopharmaceutical.

Repeated administration of the preparation
In the case of a need for repeated examination, clinical indications and potential adverse events should be considered.

4.5 Interaction with other medicinal products and other forms of interactions
In patients subjected to diagnostic examinations with use of ^{99m}Tc-Tektrotyd, somatostatin analogues should be withdrawn (both ñcoldò and labelled radioactive isotopes)
- short acting analogues ï at least 3 days before the planned examination,
- long acting analogues:
    - lanreotide ï at least 3 weeks
    - octreotide ï at least 5 weeks before the planned examination.

The specific studies concerning interaction with other drugs have not been carried out. There are limited data concerning possible interactions.

4.6 Pregnancy and lactation

Pregnancy
The absolute contraindication for use of the preparation is pregnancy. If there is a need for administration of a radiopharmaceutical to women of child-bearing age, pregnancy should be excluded. Examination in women of child-bearing age should be conducted during the first days (about 10 days) after menstruation. Each woman in whom menstruation is delayed should be (until the exclusion) regarded pregnant. Other diagnostic methods, not requiring administration of a radioactive agent, should be considered.

Breastfeeding
Breastfeeding should be stopped after administration of a radiopharmaceutical dose for at least 72 hours due to possible hazard to childôs health. Breastfeeding may be restarted when a radioactivity dose, which may be absorbed by the child during breastfeeding and contact with the mother, falls within legally determined limits.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
Very rarely, after administration of ^{99m}Tc-Tektrotyd, transient headache or epigastric pain may occur. Exposure to radioactivity in the case of each patient must be justified by benefits resulting from conducted examination. Administered radioactivity should be such that the radiation dose received by the patient is possibly low while obtaining desired diagnostic effect.
Exposure to ionizing radiation is potentially related to induction of neoplasm and potential risk of hereditary lesions. In case of radio diagnostic examinations the risk is minor in relation to the use of low doses of radiation.

4.9 Overdose
No case of overdose has been reported.
In case of diagnostic doses, the risk resulting from overdose may be ignored. Conduct in the case of overdose consist in maintaining vital functions. The dose absorbed by the patient may be reduced by accelerating radionuclide excretion from the organism by hydrating of the patient and frequent urination.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: radiopharmaceuticals for cancer diagnostics
ATC code: V09IA0X

5.2 Pharmacokinetic properties
After intravenous administration, ^{99m}Tc-Tektrotyd is readily removed from blood and just after 10 minutes, accumulation of a marker is seen in main organs, i.e. in the liver, spleen and kidneys as well as in tumours expressing somatostatin receptors. These changes are seen better after 2 and 4 hours while radioactivity accumulated in muscles and circulating blood decreases. After 24 hours, cancer lesions are still seen, at this

time, slight excretion by alimentary tract is observed. Maximal values of the ratio of tumour/background are observed 4 hours after injection. Values of the ratio tumour/liver and tumour/lungs are at the level of 1.4 and 12, respectively.
The preparation is excreted mainly by the kidneys and to a lesser extent, by the liver. ^{99m}TcTektrotyd is readily eliminated from blood. The activity accumulated in blood cells is below 5% regardless of injection time. Blood proteins bound is lower at earlier time points (e.g. 2% - 11% within 5 minutes after injection) compared to further time points (33% - 51% after 20 hours). Cumulative excretion with the urine within 24 hours falls within a range of 24% - 64% of the administered dose.

5.3 Preclinical safety data
Examination of harmlessness of ^{99m}Tc-Tektrotyd carried out in mice according to F.P. VI showed that solution of the radiopharmaceutical ^{99m}Tc-Tektrotyd is harmless in the studied maximal injection dose: 0.2 mg of Tetrotyd/kg body weight and 974 MBq/kg body weight. Mean increase of body weight after two days was about 11%.
Clinical trials concerning influence of the preparation on fertility and studies of carcinogenicity have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tricine (N-[Tris(hydroxymethyl)methyl]glycine, tin (II) chloride dihydrate, mannitol, EDDA (ethylenediamino-N,Nô-diacetic acid, disodium hydrogen phosphate dodecahydrate, sodium hydroxide. Nitrogen ï gas filling the vials.

6.2 Incompatibilities
Studies concerning incompatibilities of this preparation have not been carried out. ^{99m}TcTektrotyd should not be mixed with other pharmaceutical products. It is recommended to administer the preparation by a separate intravenous cannula.

6.3 Shelf life
Shelf life of the kit: 12 months
Labelled product should be administered within 6 hours after preparation. Data on radiochemical purity and stability of the preparation concern the above mentioned time at ambient temperature below 25°C.

6.4 Special precaution for storage
Keep the kit in a refrigerator at 2°C - 8°C.
Expiry date is indicated on the package.
After labelling, the prepared preparation should not be stored longer than for 6 hours, at the temperature below 25°C in a shield absorbing the ionizing radiation. The method of radiopharmaceuticals storage should be in compliance with binding regulations.

6.5 Nature and content of the container
The container contains the kit of two glass vials (Vial I and Vial II) of 10 ml volume with powder for solution for injection. Each vial is closed with a rubber stopper and an aluminium cap. The vials are packed in carton boxes. Vials I and II contain components for preparation of a radiopharmaceutical ^{99m}Tc-Tektrotyd. Nitrogen ï gas filling the vial.
Vials I: Hynic-[D-Phe1, Tyr3-Octreotide] TFA, tin(II) chloride dihydrate, tricine (N[Tirs(hydroxymethyl) methyl]glycine), mannitol,
Vial II: EDDA (ethylenediamino-N,Nô-diacetic acid, disodium hydrogen phosphate dodecahydrate, sodium hydroxide. Nitrogen ï gas filling the vial.

6.6 Special precautions for disposal and other handling
See section 12.

7. MARKETING AUTHORISATION HOLDER
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8. MARKETING AUTHOROSATION NUMBER
11664

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION
29.04.2004/03.12.2008

10. DATE OF REVISION OF THE TEXT
07.11.2009

11. DOSIMETRY
Disintegration of technetium-99m is accompanied by emission of gamma radiation of 140 keV energy. Equivalent of effective dose (EDE) after administration of ^{99m}Tc-Tektrotyd of radioactivity 740 MBq is about 4.2 mSv (in a patient weighing 70 kg). Half-life of technetium-99m is short and is 6 hours, in relation to the above, in 60 hours after administration of the preparation, less than 0.1% of the administered dose remains in the patientôs body.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
Any unused product, containers and waste material being in contact with radioactive substance should be disposed of in accordance with the local requirements. The kit for preparation of the radiopharmaceutical ^{99m}Tc-Tektrotyd is intended for labelling with technetium-99m in the form of sodium technetate (VII) [^{99m}Tc] in order to prepare ^{99m}Tc-Tektrotyd, solution for injection.

Labelling procedure:
Administration of a radioactive drug poses risk for

contamination of outsiders, e.g. with urine or vomits of the patient. Rules of radiological protection should be obeyed, and radioactive waste should be disposed according to binding rules.
During preparation and stirring of the components, rules of asepsis should be obeyed. The person preparing the drug should use rubber gloves, and vials or syringes should be placed behind anti-radiation shield. Radioactivity of the preparation ^{99m}Tc-Tektrotyd should be measured just before administration.

1. For labelling, eluate of sodium technetate (VII) [^{99m}Tc] obtained not longer than two hours before starting of labelling should be used. 99Mo/^{99m}Tc generator should be eluated within the past 24 hours.
2. Place Vial I in shield container
3. To the Vial II, inject with a syringe 1 ml of water for injection. Stir gently the content of the vial to complete dissolution of the components. From solution prepared in this way, take 0.5 ml and inject with a syringe to the Vial I. After thorough stirring, inject to the same vial (Vial I) with a syringe in an anti-radiation shield, desired radioactivity of sodium technetate (VII) [^{99m}Tc] in the amount to 2200 MBq at maximum, of the volume to 1 ml at maximum. Before removal of the needle from the vial, a volume of gas equivalent to the volume of introduced solutions should be taken with a syringe so that the pressure inside the vial is even with the atmospheric pressure. Shake the Vial I placed in the shield carefully for about 10 seconds so that the content completely dissolves.
4. Place the vial immediately in a water bath or heating block of 80°C for 20 minutes keeping the vial in a vertical position. The water bath or heating block should be placed behind appropriate anti-radiation shield. After the end of heating, the vial should be placed in the shield again and left at room temperature for at least 30 minutes in order to cool the preparation. The vial should not be cooled in cold water because it may influence the process of labelling of the preparation.
5. Label the total radioactivity, fill in the provided label and stick to the vial.
6. Drugs intended for parenteral administration should be inspected visually before administration. Presence of insoluble particles or improper colour of the solution should be excluded. In order to do this, before intravenous administration, stirred vial content should be examined through glasses of lead glass, keeping a safe distance. The preparation should not be administered if the solution is not clear or contains no dissolved particles.
7. The vial with the labelled preparation should be kept in a vertical position, at the temperature from 15°C to 25°C. Use within 6 hours after preparation.

Caution

1. The volume of sodium technetate (VII) [^{99m}Tc] solution, added to Vial I of the kit for preparation of radiopharmaceutic ^{99m}Tc-Tektrotyd should not exceed 1 ml.
2. To the Vial I, a maximum of 2200 GBq of technetate-99m may be added. The amount of a dose of radioactivity is calculated with consideration of administration time of the preparation to the patient so that the activity of the whole vial falls within a range of 740 ï 1200 MBq at the moment of administration.
3. If the radioactive concentration of labelled preparation is too high, the preparation may be diluted after labelling to a maximum of 3 ml with normal saline. The volume of added solution should not be increased before stirring.
4. The preparation administered during the examination shows radiochemical purity above 90% measured by ITLC method directly before injection.
5. The content of the vials of the kit for reparation of a radiopharmaceutical ^{99m}TcTektrotyd is not radioactive. After addition of solution of sodium technetate (VII) [^{99m}Tc-Tekrotyd], proper anti-radiation shield should be used.
6. The course of labelling of ^{99m}Tc-Tektrotyd depends on maintenance of tin(II) chloride compound in a reduced state. The presence of oxidizer in the solution of sodium technetate (VII) [^{99m}Tc] may negatively influence the quality of the labelled preparation.
7. The content of the kit for preparation of the radiopharmaceutical ^{99m}Tc-Tektrotyd is sterile. The vials do not contain bacteriostatic agents. Preparation of the radiopharmaceutical ^{99m}Tc-Tektrotyd should take place in aseptic conditions, according to the provided instruction.

Instruction of quality control

Determination of radiochemical purity may be carried out with the use of the described chromatographic procedures.

Equipment and reagents

1. two plates of Gelman ITLC SG type (2 cm x 10 cm)
2. two developing chambers with a cover
3. methylethylketone (MEK)
4. the mixture of acetonitrile and water in a volume ratio of 1:1 (preparation of the mixture ï see below)
5. a syringe of 1 ml volume with a needle for subcutaneous injections
6. a device for calculations

The mixture of acetonitrile and water (in a volume ratio of 1:1) (ACNW)

Mix carefully the same volumes of acetonitrile and water. The mixture should be prepared every day.

The method of determination

1. Fill in the developing chambers with the prepared solutions of MEK and ACNW to the height of 0.5 cm. Cover the chambers and wait for the balancing of concentrations of pair of both solutions.
2. Mark with a pencil on strips of Gelman ITLC SG type the section of 1 cm from their bottom margin (the place of putting a drop of analysed preparation) and a section of 0.5 cm from their upper margin (the place where head of the developing solution will move).
3. With the use of a needle for subcutaneous injections, place the drop (about 5 ï 10 µl) of the solution of ^{99m}Tc-Tektrotyd at the centre of the line determining the distance of 1 cm of the bottom margin of each strip not allowing to its drying. REMARK: Do not touch the surface of the strip with a needle.
4. Place the chromatographic chambers behind the lead anti-radiation shield.
5. Place one ITLC SG strip in a chamber with a MEK solution and another ITLC SG strip in ACNW solution. The strip should be placed in a vertical position, the place of putting of a drop of ^{99m}Tc-Tektrotyd should be above the level of solution surface, the upper end of the strip should be leaned against the rim of the container. REMARK: the strip surface may not touch the walls of the container. The container should be covered.
6. Wait until the head of the solution moves to the line determining the distance of 0.5cm from the upper margin of the strip.
7. Remove the strips from the containers and dry (behind the anti-radiation shield).
8. Cut the strips by a method described below:
   ITLC SG MEK: in the middle between the head of the solution and the line determining the place of putting the drop of the preparation (Rf = 0.5 to 1.0)
   ITLC SG ACNW: in a distance of 3.5 cm from the bottom margin of the strip (Rf = 0 to 0.3).
9. Measure the radioactivity of each part of the strip and carry out the calculations presented below:

   Percent of technetate (VII) [^{99m}Tc] = A

$$A = 100 \times \frac{\text{Radioactivity of the upper section of the strip ITLC SG MEK (Rf 0.5 to 1.0)}}{\text{Total radioactivity of both parts of ITLC SG MEK strip}}$$

   Percent of technetate [^{99m}Tc], not moved material = B

$$B = 100 \times \frac{\text{Radioactivity of the lower section of the strip ITLC SG ACNW (Rf 0 to 0.3)}}{\text{Total radioactivity of both parts of ITLC SG ACNW strip}}$$

10. Percent of the content of complex ^{99m}Tc-Tekrotyd : 100 ï (A +B). In the properly prepared preparation, ready for administration to the patient, the content of the complex should be at least 90%.