TEKTROTYD
Kit for radiopharmaceutical preparation

Imaging of somatostatin receptors

Specificity
Precision
Efficiency
Convenience
Tc^{99m} labelling

www.polatom.pl
Globally available for somatostatin receptor targeting

Marketing Authorization:

- **TEKTROTYD 20 µg:**
  Bulgaria, Czech Republic, Denmark, Estonia, Finland, Hungary, Malta, Norway, Poland, Romania, Slovakia, Sweden,
- **TEKTROTYD 16 µg:**
  Greece, Costa Rica, Columbia, Cyprus.

- **TEKTROTYD 16 µg** distribution via ROTOP Pharmaka (as MAH):
  Austria, France, Germany, Great Britain, Italy, Portugal, Spain.

Central & South America
Pharmaceutical form

Kit for radiopharmaceutical preparation
White or almost white lyophilisates
For radiolabelling with sodium pertechnetate (99mTc) solution

Clinical particulars

Therapeutic indications

This medicinal product is for diagnostic use only. After radiolabelling with sodium pertechnetate (99mTc) solution, the solution of 99mTc-Tektrotyd obtained is indicated for use in adults as adjunct in the diagnosis and management of somatostatin receptor bearing neuroendocrine tumours (NET), by aiding their localization.

Tumours which do not bear somatostatin receptors will not be visualised, see section „Image interpretation“.

Posology and method of administration

Posology

Adults

The suggested activity range is 370 to 740 MBq in one single intravenous injection. The activity to be administered depends on the available equipment.

Elderly population (above 65 years)

No dose adjustment is required for elderly.

Renal impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients, see section „Special warnings and precautions for use“. 

Hepatic impairment

Dosage reduction in hepatic impairment is not necessary, see section „Pharmacokinetic properties“.

Paediatric population

There are no data on safety and efficacy of 99mTc-Tektrotyd for the use in paediatric patients.

If alternative techniques not using ionising radiation are not available, the use in children and adolescents has to be considered carefully, based on clinical needs and assessing the risk/benefit ratio in this patient group. Because of the potential hazard of ionising radiation, 99mTc-Tektrotyd should not be used in children under 18 years of age, unless the value of the expected clinical information is considered to outweigh the possible risk from radiation.

Method of administration

This medicinal product should be radiolabelled before administration to the patient. For instructions for preparation of the radiopharmaceutical, see section „Instructions for preparation of radiopharmaceuticals“. 

99mTc-Tektrotyd is administered intravenously in a single dose.

For patient preparation, see section „Special warnings and precautions for use“.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely diagnostic benefit and risk from radiation exposure.

For more convenient administration, the solution of 99mTc-Tektrotyd may be diluted with sodium chloride injection, see section „Incompatibilities“. 

Image acquisition

Image acquisition should be carried out at 1-2 and 4 hours after intravenous administration. Images at 1-2 hours post-injection may be useful for comparison and evaluation of abdominal activity imaged at 4 hours.

The examination may be complemented, depending on the clinical need, by acquisition 15 minutes and 24 hours post-injection of the tracer. It is recommended to carry out the examinations using whole body technique and SPECT (or SPECT/CT) of selected body areas.

Contraindications

Hypersensitivity to HYNIC-[D-Phe3, Tyr3-Octreotide] trifluoroacetate or to any of the excipients or sodium pertechnetate (99mTc) solution for injection.

Pregnancy.

In case of breastfeeding, see section „Fertility, pregnancy and lactation“. 

Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions.

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Renal impairment

Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients. In patients with significant renal failure the administration of 99mTc-Tektrotyd is not advisable. The reduced or absent function of the principal route of excretion will lead to a higher radiation exposure.

Administration should be considered only when the possible risk from radiation is outweighed by the potential diagnostic information. Interpretable scintigrams may be obtained after haemodialysis during which the high background activity can at least partially be removed. After dialysis a higher than usual uptake in liver, spleen and intestinal tract, and a higher than usual activity in circulation might be observed.

Hepatic impairment

Dosage reductions in hepatic impairment are not necessary, see section „Pharmacokinetic properties“. 

Paediatric population

For information on the use in paediatric population, see section „Posology and method of administration“. 

Patient preparation

The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination in order to reduce radiation.

Optimal imaging of the abdominal cavity is obtained after the application of liquid diet starting two days before the examination as well as administration of laxatives on the day before the examination. The method of patient preparation may depend on the applied examination protocol and the localization of imaged lesions.

Regarding patients on octreotide therapy it is recommended to withdraw this therapy temporarily to avoid a possible blockade of somatostatin receptors. This recommendation is given on empirical grounds, the absolute need for such measure has not been demonstrated. In some patients the withdrawal of therapy might not be tolerated and may cause rebound effects. This is notably the case in insulinoma patients, where the danger of sudden hypoglycaemia must be considered, and in patients suffering from the carcinoid syndrome (for proposals for withdrawal refer to section „Interaction with other medicinal products and other forms of interaction“).

Caution should be exercised when administering 99mTc-Tektrotyd to patients with diabetes mellitus and more frequent monitoring of glucose level can be considered after its administration due to various inhibition of hyper- or hypoglycaemic hormones by somatostatin analogs.

Image interpretation

Positive scintigraphy with 99mTc-Tektrotyd reflects the presence of an increased density of tissue somatostatin receptors rather than a malignant disease. Tumours which do not bear receptors will not be visualised. In some patients suffering from insulinoma the tumour cannot be visualised. This is notably the case in insulinoma patients, where the danger of sudden hypoglycaemia must be considered, and in patients suffering from the carcinoid syndrome (for proposals for withdrawal refer to section „Interaction with other medicinal products and other forms of interaction“).

An increase in somatostatin receptor density can also occur in the following situations:

- Patients suffering from lymphoma, multiple myeloma, chronic lymphocytic leukaemia, Hodgkin’s disease, non-Hodgkin lymphomas, the possibility of uptake in lymphocyte concentrations (subacute inflammations) must be considered.

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Adverse effects attributable to the administration of Tektrotyd are very rare (< 1/10,000). Rare (≥ 1/10,000 to < 1/1,000)

During the evaluation of adverse reactions the following frequency data are taken as a basis:
- short acting analogues – at least 2 days before the planned examination,
- long acting analogues: lanreotide – at least 3 weeks
- octreotide – at least 5 weeks before the planned examination.

The withdrawal of therapy with somatostatin analogues as a preparatory step to scintigraphy might provoke severe adverse effects, generally of the nature of a return of the symptoms seen before therapy was started.

No interaction studies have been performed. There are limited data concerning possible interactions.

Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of a radiopharmaceutical to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Breast-feeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 24 hours and the expressed feeds discarded.

Fertility
No studies on fertility have been performed.

Effects on ability to drive and use machines
Effects on the ability to drive or use machines have not to be expected after use of this product.

Undesirable effects
During the evaluation of adverse reactions the following frequency data are taken as a basis:
- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1,000 to < 1/100)
- rare (≥ 1/10,000 to < 1/1,000)
- very rare (< 1/10,000)
- not known (cannot be estimated from the available data)

Adverse effects attributable to the administration of Tektrotyd are very rare (< 1/10000). Transient headache or epigastric pain may occur directly after administration.

Exposure to ionisation radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is about 3.6 mSv when the maximal recommended activity of 740 MBq is administered these adverse events are expected to occur with a low probability.

Interaction with other medicinal products and other forms of interaction
In patients subjected to diagnostic examinations with the use of 
\(^{99m}\text{Tc}\)-Tektrotyd, the treatment with somatostatin analogues should be withdrawn temporarily (both "cold" as well as labelled with radioactive isotopes): short acting analogues at least 2 days before the planned examination, long acting analogues: lanreotide at least 3 weeks, octreotide at least 5 weeks before the planned examination.

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Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products At. Jerozolimskie 181C 02-222 Warszawa
Tel.: + 48 22 49 21 301
Faks: + 48 22 49 21 309
e-mail: ndi@upr.gov.pl

Adverse reactions may be reported to marketing authorization holder.

Overdose

No case of overdose has been reported. Overdose is unlikely when the radiopharmaceutical is administered by diagnostic monodose injection.

In the event of administration of a radiation overdose with 
\(^{99m}\text{Tc}\)-Tektrotyd the adsorbed dose to the patient should be reduced by increasing the elimination of the radionuclide from the body by administration of liquids and frequent bladder voiding.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Diagnostic radiopharmaceuticals, tumour detection, technetium (\(^{99m}\text{Tc}\)) compounds;
ATC code: V09IA07

Pharmacodynamic effects

At the chemical concentrations used for diagnostic examinations 
\(^{99m}\text{Tc}\)-Tektrotyd does not appear to have any pharmacodynamic activity.

Pharmacokinetic properties

Distribution
After intravenous administration, 
\(^{99m}\text{Tc}\)-Tektrotyd is rapidly eliminated from the blood. Already after 10 minutes, accumulation of 
\(^{99m}\text{Tc}\)-Tektrotyd is seen in the main organs, i.e. liver, spleen and kidneys as well as in tumours expressing somatostatin receptors.

Uptake
Maximal values of the tumour/background ratio are observed at 4 hours after injection. Cancer lesions are still visible after 24 hours. Slight excretion by the alimentary tract is observed in late images.

Elimination
The activity is excreted mainly by the renal route with a small contribution of hepatic excretion. 
\(^{99m}\text{Tc}\)-Tektrotyd is rapidly eliminated from the blood. The activity accumulated in the blood cells is below 5% regardless of time after injection.

Radiation half-life
\(^{99m}\text{Tc}\) decays to technetium-99 with a half-life of about 6 hours.

Preclinical safety data

There is limited preclinical experience from the use of 
\(^{99m}\text{Tc}\)-Tektrotyd. No testing has been performed on repeated dose toxicity, carcinogenic potential, fertility or developmental toxicity. A genotoxicity test showed a negative result in the bacterial reverse mutation assay suggesting that the kit for preparation of 
\(^{99m}\text{Tc}\)-Tektrotyd is non-mutagenic.

PHARMACEUTICAL PARTICULARS

List of excipients

Vial:
N\{tris(hydroxymethyl)methyl\}glycine (Tricine)
Stannous chloride dihydrate
Mannit
Sodium hydroxide for pH adjustment
Hydrochloric acid for pH adjustment
Nitrogen (protective gas)

Vial II:
Ethylene diamine-N,N'-diacetic acid (EDDA)
Disodium phosphate dodecahydrate
Sodium hydroxide
Sodium hydroxide for pH adjustment
Hydrochloric acid for pH adjustment
Nitrogen (protective gas)

Incompatibilities
After radiolabelling a dilution with up to 5 ml physiological saline is possible. 99mTc-Tektroyd must not be mixed with other medicinal products.

Shelf life
1 year.
After reconstitution and radiolabelling 4 hours when stored below 25°C.

Special precautions for storage
Store in a refrigerator at 2°C - 8°C. During transportation (not longer than 5 days) up to 35°C.
For storage conditions after radiolabelling of the medicinal product, see section „Shelf life“.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

Nature and content of the container
Glass vials (Type I Ph. Eur.) of 10 mL nominal capacity, sealed with a bromobutyl stopper and an aluminium cap.
The aluminium cap for vial I is blue and the aluminium cap for vial II is white in order to distinguish vial I from vial II during the reconstitution/radiolabelling procedure.
Vials I and II contain components for the radiopharmaceutical preparation of 99mTc-Tektroyd.
Each vial contains a white or nearly white lyophilisate for preparation of a solution for injection.

Vial I: Active substance: HYNIC-[D-Phe1, Tyr2-Octreotide] trifluoroacetate, excipients: stannous chloride dihydrate, N-N'Tris(hydroxymethyl)methyl]glycine (tricine), mannit, sodium hydroxide or hydrochloric acid for pH adjustment, nitrogen
Vial II: Excipients: ethylene diamine-N,N'-diacetic acid (EDDA), disodium phosphate dodecahydrate, sodium hydroxide, sodium hydroxide or hydrochloric acid for pH adjustment, nitrogen
Pack size: 2 vials

Special precautions for disposal and other handling
Tektroyd is supplied as kit consisting of two vials which cannot be used separately.
The radionuclide is not part of the kit.

General warning
After radiolabelling of Tektroyd the common protective measures for radioactive medicinal product must be applied.
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the competent official organisation.
Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.
Contents of the vials are intended only for use in the preparation of 99mTc-Tektroyd and are not to be administered directly to the patient without first undergoing the preparative procedure.
For instructions on radiolabelling of the medicinal product before administration, see section „Instructions for preparation of radiopharmaceuticals“.
If at any time in the preparation of this product the integrity of the vial is compromised, the product should not be used.
Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before extemporary preparation is not radioactive. However, after sodium pertechnetate (99mTc) injection, Ph. Eur is added, adequate shielding of the final preparation must be maintained.
The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**DOSIMETRY**

Technetium (99mTc) is obtained from a 99Mo/99mTc radionuclide generator and decays by gamma emission (energy 141 keV) with a physical half-life of 6.02 hours to technetium-99, which in view of its long half-life of 2.13 x 10^4 years may be regarded as quasi stable.
Grimes et al. (2011), performed patient-specific dosimetry of 99mTc-Tektroyd in NETs with the OLINDA/EXAM software with time-integrated activity coefficients estimated from a hybrid planar/SPECT technique. The average organ absorbed doses and effective dose of 99mTc-Tektroyd are given in the table below.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Dose absorbed per unit activity administered (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.0060 ± 0.0015</td>
</tr>
<tr>
<td>Brain</td>
<td>0.0022 ± 0.0005</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.0021 ± 0.0005</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>0.0062 ± 0.0017</td>
</tr>
<tr>
<td>LLI Wall</td>
<td>0.0038 ± 0.0007</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>0.0041 ± 0.0008</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.0049 ± 0.0012</td>
</tr>
<tr>
<td>ULI Wall</td>
<td>0.0042 ± 0.0009</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.0050 ± 0.0009</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.0208 ± 0.0068</td>
</tr>
<tr>
<td>Liver</td>
<td>0.0118 ± 0.0046</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.0036 ± 0.0009</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.0030 ± 0.0006</td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.0042 ± 0.0007</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.0071 ± 0.0019</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.0030 ± 0.0006</td>
</tr>
<tr>
<td>Osteogenic Cells</td>
<td>0.0079 ± 0.0016</td>
</tr>
<tr>
<td>Skin</td>
<td>0.0019 ± 0.0004</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.0296 ± 0.0121</td>
</tr>
<tr>
<td>Testes</td>
<td>0.0024 ± 0.0004</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.0029 ± 0.0006</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.0040 ± 0.0006</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>0.0142 ± 0.0039</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.0045 ± 0.0008</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.0035 ± 0.0007</td>
</tr>
</tbody>
</table>

Effective Dose (mSv/MBq) = 0.0051 ± 0.0010

The effective dose resulting from the administration of a maximum recommended activity of 740 MBq for an adult weighing 70 kg is about 3.8 mSv. For an administered activity of 740 MBq the typical radiation dose to the critical organ, i.e. the kidneys, is 15.4 mSv.

**INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS**

Withdrawals should be performed under aseptic conditions.
Usual safety precautions for the handling of radioactive materials should be followed.
The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.
If the integrity of this vial is compromised, the product should not be used.
Method of preparation

The kit consists of 2 vials:
Vial I with the active ingredient HYNIC-[D-Phe³,Tyr⁷-Octreotide] trifluoroacetate
Vial II with Ethylenediamine-N,N'-diacetic acid (EDDA) (essential excipient)
The aluminium cap for vial I is blue and the aluminium cap for vial II is white in order to
distinguish vial I from vial II during the reconstitution/radiolabelling procedure.

Preparation of technetium $^{99m}$Tc-Tektrotyd injection from the Tektrotyd kit is to be done
according to the following aseptic procedure:
1. Sanitize the closure of the two vials with a suitable alcohol swap and allow to air
   dry.
2. Add 1 mL of water for injection to the vial I using a sterile syringe. Shake gently
   for 15 seconds to ensure complete dissolution (including upside-down motions).
3. Transfer 0.5 mL coligand/buffer solution from vial II to vial I, using a sterile
   syringe, and with the same syringe withdraw an equal volume of gas in order to
   equalize the pressure. Shake gently for about 30 seconds to ensure complete
   dissolution (including upside-down motions). Vial II should be disposed after
   transfer of the solution from vial I to vial II in order to avoid mixing between vial I
   and vial II.
4. Place the vial I in a suitable shielding container.
5. Add 1 mL of sodium pertechnetate ($^{99m}$Tc) solution (up to 1,600 MBq) to vial I
   using a shielded sterile syringe and equalize the pressure. Heat the vial in a
   boiling water bath or heating block at 100°C for 10 min.
6. Leave the vial to cool down to room temperature (30 minutes). Do not speed up,
   e.g. by cool water.
7. If required, dilute the radiopharmaceutical up to 5 mL with 0.9% sodium chloride
   solution for injection.
8. Store the labelled vial at temperature below 25°C. Use within 4 hours after
   preparation.
9. Radiochemical purity should be checked prior to patient administration according
to one of the methods detailed below.

Note:
Do not use the radiopharmaceutical if the radiochemical purity is less than 90%.

10. Dispose any unused material and its container via an authorised route.

Caution

The labelling of TEKTROTYD depends on maintenance of stannous chloride dihydrate
in its reduced state. The content of the kit for preparation of the radiopharmaceutical
Tc-Tektrotyd is sterile. The vials do not contain bacteriostatic agents.

Quality control

Determination of radiochemical purity should be performed using chromatographic
procedure described below.
Procedure. Thin-layer chromatography

Equipment and eluents
1. Two ITLC SG strips (ca. 1.5 cm x 10-12 cm): Silica gel impregnated glass fibre
   strips
2. Two developing chambers with covers
3. Solvents:
   - Methylthelketone (MEK) for impurity A, pertechnetate ($^{99m}$Tc)
   - Mixture of acetonitrile and water in a volume ratio of 1:1 (ACNW) for impurity B,
     technetium ($^{99m}$Tc) in colloidal form: Mix carefully the same volumes of acetonitrile
     and water.
     The mixture should be prepared every day.
4. 1 mL syringe with a needle for subcutaneous injections
5. Suitable counting equipment (e.g. scintillation counter, dose
   calibrator, gamma camera)

Method

1. Fill in the developing chambers with the prepared solutions of MEK and ACNW to
   the height of not more than 0.5 cm. Cover the chambers and allow to equilibrate
   with the solvents vapors.
2. Mark two ITLC SG strips with a pencil at 1.5 cm from their bottom margin (the
   place of putting a drop of analyzed preparation) and a section of 0.5 cm from
   their upper margin (the place where front of the developing solution will move).
3. Spot the drop (about 5 µl) of the solution of $^{99m}$Tc-Tektrotyd for injection using a
   needle for subcutaneous injections, in the middle of the line marked at 1.5 cm of
   the bottom margin of each strip, do not allow the spots to dry. CAUTION: Do not
   touch the surface of the strip with a needle.
4. Place the chromatographic chambers behind the lead shielding.
5. Place one ITLC SG strip in a chamber with MEK and another ITLC SG strip in
   ACNW solution. Place the strips upright to ensure that the place of spotting $^{99m}$Tc-
   Tektrotyd is above the solution line, the upper end of the strip leaned against the
   side of the chamber.

Determination of radiochemical purity should be performed using one of the methods
detailed below.

TLC with MEK:

$$A = \frac{[^{99m}\text{Tc}]\text{pertechnetate} \times 100\%}{\text{Activity both pieces}}$$

$$R_1 = 0.8 \text{ to } 1.0$$

TLC with ACNW:

$$B = \frac{[^{99m}\text{Tc}]\text{Tc in colloidal form} \times 100\%}{\text{Activity both pieces}}$$

$$R_2 = 0 \text{ to } 0.1$$

11. Calculate the percentage of radioactivity of $^{99m}$Tc-Tektrotyd using the following
    formula: 100% – (A+B). Limit: minimum 90 per cent of the total activity.

Pharmacologic evaluations:

- **TEKTROYD 16 µg**
  - Distribution via ROTOP Pharmaka (as MAH):
    - Austria, France, Germany, Great Britain, Italy, Portugal, Spain.

- **TEKTROYD 20 µg**
  - Distribution via ROTOP Pharmaka (as MAH):
    - Austria, France, Germany, Great Britain, Italy, Portugal, Spain.

**Central & South America**

**Pharmacologic evaluations:**

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