SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tektrotyd,

20 micrograms, kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vial I contains 20 micrograms of
HYNIC-[D-Phe^{1},Tyr^{3}-Octreotide] trifluoroacetate
The radionuclide is not part of the kit.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation
White or almost white lyophilisates
For radiolabelling with sodium pertechnetate (^{99m}Tc) solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the solution of ^{99m}Tc-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 4.4, „image interpretation").

4.2 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 4.4.
Hepatic impairment
Dosage reduction in hepatic impairment is not necessary, see section 5.2.
Paediatric population
There are no data on safety and efficacy of ^{99m}Tc-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 upon clinical needs and assessing the risk/benefit ratio in this patient group. Because of the potential hazard of ionising radiation, ^{99m}Tc-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 12.
^{99m}Tc-Tektrotyd is administered intravenously in a single dose.
For patient preparation, see section 4.4.
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 ^{99m}Tc-Tektrotyd may be diluted with sodium chloride injection, see section 6.2
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.

4.3 Contraindications

Hypersensitivity to HYNIC-[D-Phe^{1},Tyr^{3}-Octreotide] trifluoroacetate or to any of the excipients or sodium pertechnetate (^{99m}Tc) solution for injection.
Pregnancy.
In case of breastfeeding, see section 4.6.

4.4 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 ^{99m}Tc-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 5.2.
Paediatric population
For information on the use in paediatric population, see 4.2.
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 4.5).
Caution should be exercised when administering ^{99m}Tc-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- of hypoglycaemic hormones by somatostatin analogs.
Image interpretation
Positive scintigraphy with ^{99m}Tc-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 a number of patients suffering from gastro-entero-pancreatic neuroendocrine or carcinoid tumours the receptor density is insufficient to allow visualisation with ^{99m}Tc-Tektrotyd. Notably in approximately 50% of patients suffering from insulinoma the tumour cannot be visualised.
Furthermore positive uptake is not specific for gastro-entero-pancreatic- and carcinoid-tumours. Positive scintigraphic results require evaluation of the possibility that another disease, characterised by high local somatostatin receptor concentrations, may be present. An increase in somatostatin receptor density can also occur in the following pathological conditions: tumours arising from tissue embryologically derived from the neural crest, (paragangliomas, medullary thyroid carcinomas, neuroblastomas, pheochromocytomas), tumours of the pituitary gland, endocrine neoplasms of the lungs (small-cell carcinoma), meningiomas, mammary carcinomas, lympho-proliferative disease (Hodgkin's disease, non-Hodgkin lymphomas), and the possibility of uptake in areas of lymphocyte concentrations (subacute inflammations) must be considered.
If the patient is not prepared properly to the examination, bowel uptake might influence the quality of images. Significant nonspecific accumulation occurring within digestive tract could be misinterpreted and misreported as pathologic or could impair the proper images evaluation.
After the procedure.
Close contact with infants and pregnant women should be avoided during the first 24 hours after administration of the radiopharmaceutical.
General warnings
Contents of the kit vials are intended only for use in the preparation of ^{99m}Tc-Tektrotyd and are not to be administered directly to a patient without first undergoing the preparative procedure.

Specific warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.
Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction
In patients subjected to diagnostic examinations with the use of ^{99m}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.

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 this therapy was started.
No interaction studies have been performed. There are limited data concerning possible interactions.

4.6 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.
Pregnancy
The use of ^{99m}Tc-Tektrotyd is contraindicated in pregnant women due to the potential radiation risk incurred by the mother and the foetus (see section 4.3).
Breast-feeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of 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.

4.7 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.

4.8 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 form 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 3.8 mSv when the maximal recommended activity of 740 MBq is administered these adverse events are expected to occur with a low probability.
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
Al. Jerozolimskie 181C
02-222 Warszawa
Tel.: + 48 22 49 21 301
Faks: + 48 22 49 21 309
e-mail: ndl@urpl.gov.pl
Adverse reactions may be reported to marketing authorization holder.

4.9 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}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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Diagnostic radiopharmaceuticals, tumour detection, technetium (^{99m}Tc) compounds;
ATC code: V09IA07
Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations ^{99m}Tc-Tektrotyd does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties
Distribution
After intravenous administration, ^{99m}Tc-Tektrotyd is rapidly eliminated from the blood. Already after 10 minutes, accumulation of ^{99m}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}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}Tc decays to technetium-99 with a half-life about 6 hours.

5.3 Preclinical safety data
There is limited preclinical experience from the use of ^{99m}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}Tc-Tektrotyd is non-mutagenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Vial I:
N-[tris(hydroxymethyl)methyl]glycine (Tricine)
Stannous chloride dihydrate
Mannitol
Sodium hydroxide for pH adjustment
Hydrochloric acid for pH adjustment
Nitrogen (protective gas)
Vial II:
Ethylenediamine-N,N'-diacetic acid (EDDA)
Disodium phosphate dodecahydrate
Sodium hydroxide
Sodium hydroxide for pH adjustment
Hydrochloric acid for pH adjustment
Nitrogen (protective gas)

6.2 Incompatibilities
After radiolabelling a dilution with up to 5 ml physiological saline is possible. ^{99m}Tc-Tektrotyd must not be mixed with other medicinal products.

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

6.4 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 6.3. Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 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 ^{99m}Tc-Tektrotyd.

Each vial contains a white or nearly white lyophilisate for preparation of a solution for injection.

Vial I: Active substance: HYNIC-[D-Phe^{1}, Tyr^{3}-Octreotide] trifluoroacetate, excipients: stannous chloride dihydrate, N-[Tris(hydroxymethyl)methyl] glycine (tricine), mannitol, sodium hydroxide or hydrochloric acid for pH adjustment, nitrogen

Vial II: Excipients: ethylenediamine-N,N'-diacetic acid (EDDA), disodium phosphate dodecahydrate, sodium hydroxide, sodium hydroxide or hydrochloric acid for pH adjustment, nitrogen
Pack size: 2 vials

6.6 Special precautions for disposal and other handling
Tektrotyd 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 Tektrotyd 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 ^{99m}Tc-Tektrotyd 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 12.
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 (^{99m}Tc) 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.

7 MARKETING AUTHORISATION HOLDER
Narodowe Centrum Badań Jądrowych
ul. Andrzeja Sołtana 7
05-400 Otwock, Poland
Phone: +48 22 7180700
Fax: +48 22 7180350
e-mail: polatom@polatom.pl

8 MARKETING AUTHORISATION NUMBER(S)
23479

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 2016.10.11

10 DATE OF REVISION OF THE TEXT
2016.10.11

11 DOSIMETRY
Technetium (^{99m}Tc) is obtained from a ^{99}Mo/^{99m}Tc 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^{5} years may be regarded as quasi stable.

Grimes et al. (2011), performed patient-specific dosimetry of ^{99m}Tc-Tektrotyd 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 ^{99m}Tc-Tektrotyd are given in the table below.

Organ	Dose absorbed per unit activity administered (mGy/MBq)
	Adults
Adrenals	0.0060 ± 0.0015
Brain	0.0022 ± 0.0005
Breasts	0.0021 ± 0.0005
Gallbladder Wall	0.0062 ± 0.0017
LLI Wall	0.0038 ± 0.0007
Small Intestine	0.0041 ± 0.0008
Stomach Wall	0.0049 ± 0.0012
ULI Wall	0.0042 ± 0.0009
Heart Wall	0.0050 ± 0.0009
Kidneys	0.0208 ± 0.0068
Liver	0.0118 ± 0.0046
Lungs	0.0036 ± 0.0009
Muscle	0.0030 ± 0.0006
Ovaries	0.0042 ± 0.0007
Pancreas	0.0071 ± 0.0019
Red Marrow	0.0030 ± 0.0006
Osteogenic Cells	0.0079 ± 0.0016
Skin	0.0019 ± 0.0004
Spleen	0.0296 ± 0.0121
Testes	0.0024 ± 0.0004
Thymus	0.0029 ± 0.0006
Thyroid	0.0040 ± 0.0006
Urinary Bladder Wall	0.0142 ± 0.0039
Uterus	0.0045 ± 0.0008
Total Body	0.0035 ± 0.0007
Effective Dose (mSv/MBq)	**0.0051 ± 0.0010**

Grimes J, Celler A, Birkenfeld B, et al. Patient-Specific Radiation Dosimetry of ^{99m}Tc-HYNIC-Tyr^{3}-octreotide in Neuroendocrine Tumours. J Nucl Med 2011; 52: 1474-1481.
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.

12 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-Phe^{1},Tyr^{3}-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 II 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 II to vial I 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 technetium ^{99m}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:
   - Methylethylketone (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.
6. **CAUTION:** the strip surface may not contact the walls of the chamber. The chambers should be covered.
7. Wait until the front of the solution moves to the line determining the distance of 0.5 cm from the upper margin of the strip.
8. Remove the strips from the chambers and allow to dry behind the lead shielding.
9. Cut the strips as described below:
   ITLC SG MEK: in the middle between the front of the solution and the line determining the place of putting the drop of the preparation
   ITLC SG ACNW: in a distance of 2 cm from the bottom margin of the strip
10. Measure the radioactivity of each part of the strip and calculate the results as follows:

TLC with MEK:

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

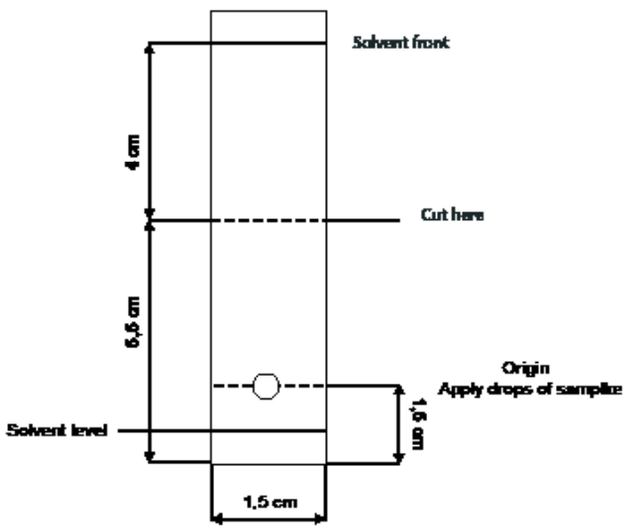
Rf = 0.8 to 1.0

TLC with ACNW:

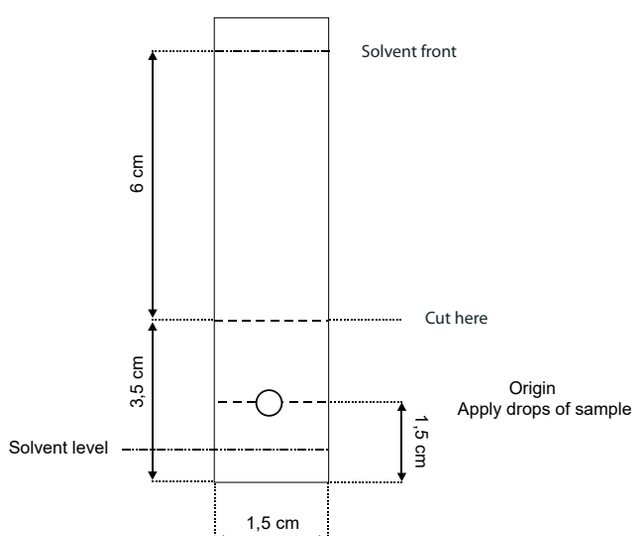
$$B = [^{99m}\text{Tc}]\text{Tc in colloidal form [\%]} = \frac{\text{Activity lower portion}}{\text{Activity both pieces}} \times 100\%$$

Rf = 0 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.



ITLC SG with MEK



ITLC SG with ACNW

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