

Public Assessment Report Scientific discussion

Tektrotyd (HYNIC-[D-Phe¹,Tyr³-Octreotide] trifluoroacetate)

SE/H/1509/01/DC

This module reflects the scientific discussion for the approval of Tektrotyd. The procedure was finalised on 2016-05-24. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Narodowe Centrum Badań Jądrowych has applied for a marketing authorisation for Tektrotyd, 20 micrograms, kit for radiopharmaceutical preparation. The active substance is HYNIC-[D-Phe¹, Tyr³-Octreotide] trifluoroacetate (diagnostic radiopharmaceuticals, tumour detection).

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC. For a well-established use (WEU) application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. In a WEU application, results of pre-clinical and clinical trials are replaced by detailed references to published scientific literature. The active substance is not considered a new active substance.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

^{99m}Tc-EDDA/HYNIC-TOC is not expected to exert any pharmacological effects when used in clinically relevant concentrations for radiodiagnostic purposes. No safety pharmacology data has been presented; however, adverse cardiovascular, CNS or respiratory effects are not expected based on the clinical experience of the product. Furthermore, since the product will be administered in a hospital setting any safety pharmacological adverse effects can be attended to clinically.

III.2 Pharmacokinetics

^{99m}Tc-EDDA/HYNIC-TOC will be administered intravenously. Distribution of the drug is similar in rats and in mice. Four hours after administration, residual activity of the drug was found mainly in the tumor and in the kidney. Urinary excretion is the main elimination pathway. Most of ^{99m}Tc-EDDA/HYNIC-TOC, eliminated by urine, is excreted within the first two hours.

III.3 Toxicology

Toxicological information on ^{99m}Tc-EDDA/HYNIC-TOC is very limited. The applicant has submitted one single dose toxicity study which has been disregarded as the present application is submitted according to the legal basis well-established use.

Several deficiencies, which would normally preclude an approval, have been identified in the non-clinical part of the dossier. However, ^{99m}Tc-EDDA/HYNIC-TOC has been in clinical use for many years and its clinical safety profile is well-known. In accordance with the Guideline on the non-clinical documentation for mixed marketing authorisation applications (CPMP/SWP/799/95), focus can be put on genotoxicity, reproductive toxicity and carcinogenicity. Since the product is intended for single use, no carcinogenicity testing is warranted. ^{99m}Tc-EDDA/HYNIC-TOC is contraindicated during pregnancy due to the potential radiation risk incurred by the mother and the fetus, and no reproductive and developmental toxicity studies are considered necessary. The genotoxicity test, which was performed in accordance with ICHS2A using the kit for preparation of ^{99m}Tc-Tektrotyd, showed a negative result in the bacterial reverse mutation assay suggesting that the product is non-mutagenic. Also, the radioactive component in the product is in itself genotoxic and the peptide dose is considered very low. Therefore, this is considered acceptable. No formal testing for local tolerance has been performed, which is considered acceptable considering the long clinical experience of the product.

III.4 Ecotoxicity/environmental risk assessment

No ERA has been performed for ^{99m}Tc-EDDA/HYNIC-TOC. However, since the product is a peptide it is therefore unlikely to result in a significant risk to the environment.

III.5 Discussion on the non-clinical aspects

In conclusion, while the non-clinical testing of ^{99m}Tc-EDDA/HYNIC-TOC is not up to the current standard, the well-established use of the product and the long clinical experience compensates for the non-clinical shortcomings.

IV. CLINICAL ASPECTS

IV.1 Introduction

Neuroendocrine tumours (NET) frequently overexpress more than one subtype of somatostatin receptors (SSTR), but SST2 (subtype SST2a) is the most frequently overexpressed (80-100%). The majority of NETs express also SST1 and SST5, followed by SST3 and very rarely SST4.

According to Reubi, (Neuroendocrinology, 2004) SST2 are present in 96% of midgut carcinomas, 100% of gastrinomas and in 70% of insulinomas, whilst pheochromocytomas express SST2 in 25 – 70% of cases. The somatostatin analogue octreotide has high affinity to SST2, but less affinity to SST5 and SST3.

“Nuclear medicine in NET” (Sorhag et al. Wien Med Wochenschr, 2012) provides an overview of the use of nuclear medicine as diagnostic tools in the work-up of patients with known or suspected NET. It covers not only the use of Octreoscan and Tektrotyd but also, for example ^{118}F -FDG PET and positron emitters such as ^{68}Ga labelled somatostatin analogues for PET and PET/CT scanning.

Poorly differentiated NET often show low receptor density and here FDG PET has a role, whilst the use of the Gallium isotope leads to better spatial resolution and better image quality. No Gallium labelled analogues are currently licensed through the centralised procedure.

IV.2 Pharmacokinetics

The active substance in Tektrotyd is HYNIC-[D-Phe¹, Tyr³-Octreotide] trifluoroacetate, (HYNIC-Tyr³-Octreotide, HYNIC-TOC), in which the eight-amino acid peptide Tyr³-Octreotide – is responsible for binding to somatostatin receptors expressed in some tissues, and particularly expressed in high density on tumor cells. The HYNIC (6- hydrazinonicotinic acid) moiety attached to Phe¹ is responsible for complexation of technetium-99m. After radiolabelling with technetium-99m the active substance in the final radioactive preparation is $^{99\text{m}}\text{Tc}$ -(EDDA)₂HYNIC-Tyr³-Octreotide.

Distribution

Plasma protein binding measured at later time points (20 h) was 33-51%, whereas it was substantially lower directly after injection (Decristoforo, Eur J Nucl Med, 2000). According to a study in 8 patients by Gonzalez-Vazquez 2006 (App. Rad.Isotopes), activity was accumulated mainly in the liver, spleen, kidneys and, in lesser quantity, in the thyroid.

Elimination

HYNIC-TOC is rapidly cleared from the circulation, with a short effective half-life. It appears as the radioactive tracer is eliminated mainly by renal excretion. Cumulative urine excretion of radioactivity over 24h has been reported to be 24-64% (Decristoforo, Eur J Nucl Med, 2000). Some gastrointestinal excretion was also observed in images, but the image quality was impaired due to low count rate at later time points.

The available PK data for HYNIC-TOC are based on measurement of radioactivity, and since $^{99\text{m}}\text{Tc}$ has a radioactivity decay half-life of around 6 h elimination later in time may not be fully characterised. In addition, it is not known if the activity in urine comes from unchanged HYNIC-TOC and/or metabolites. As HYNIC-TOC is given only as a single injection, characterisation of its elimination is however considered sufficient.

Special populations

The SmPC recommendation is not to administer Tektrotyd to patients with significant renal failure. If administered to patients with renal impairment, haemodialysis can be used to reduce the high background activity. On the other hand no dose adjustment is proposed in hepatic impairment or elderly.

^{99m}Tc-Tektrotyd has not been systematically studied in patients with renal impairment. As urinary excretion is an important route of elimination, some degree of caution is in renal impairment is reasonable. The radiation risk for patients with renal impairment is however probably lower than with ¹¹¹In-pentetreotide due to a shorter radiation half-life (6 h compared with 2.8 days) and signs of less dependency on renal elimination. The SmPC text proposed by the Applicant clarifies that “Careful consideration of the activity to be administered is required since an increased radiation exposure is possible”.

^{99m}Tc-Tektrotyd has not been systematically studied in patients with hepatic impairment. Hepatic elimination does not seem to be a major route of elimination, and therefore no restrictions in patients with hepatic impairment should be needed. No safety or PK difference between elderly and younger patients has been reported for ^{99m}Tc-Tektrotyd, and there is no need for special dose recommendations for elderly, in addition to the warning already provided for renal impairment.

Interactions

The risk for pharmacokinetic drug-drug interactions has not been addressed in the application. No interaction studies have been performed. As HYNIC-TOC is given as a single injection with short half-life, the risk for clinically relevant pharmacokinetic interactions appears to be low. The lack of data is acceptable.

IV.3 Clinical efficacy

A large number of published papers have been submitted in support of licensure. For a more detailed presentation please refer to the Clinical Assessment Report and the comprehensive Clinical Overview.

In 2003, Gabriel et al published a paper titled “An Inpatient Comparison of ^{99m}Tc-EDDA/HYNIC-TOC with ¹¹¹In-DTPA-Octreotide for Diagnosis of Somatostatin Receptor-Expressing Tumors”.

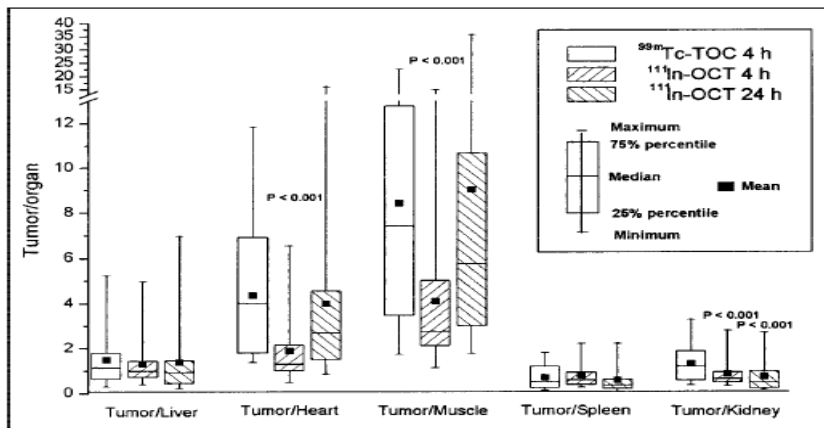
The results were summarized as follows:

TABLE 2
Scintigraphic Results of ^{99m}Tc-TOC and ¹¹¹In-OCT: Analysis per Lesion

Group	n	^{99m} Tc-TOC				¹¹¹ In-OCT			
		TP	TN	FP	FN	TP	TN	FP	FN
Detection	6	0	0	1	5	0	1	0	5
Staging	84	78	0	1	5	67	0	1	16
SSTR status	29	21	0	0	8	20	0	0	9
Follow-up	6	3	2	1	0	3	3	0	0
Overall	125	102	2	3	18	90	4	1	30

TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative.

FIGURE 5. Statistical analysis of tumor-to-organ ratios in matching studies with pathologic uptake (n = 21).



This study is a well-designed and showed increased sensitivity of Tektrotyd vs. Octreotide, but there were numerically more false positive findings (3 vs. 1). In two of these cases this referred to non-specific uptake in the bowel. Tumour/organ uptake at 4 h for Tektrotyd was at least similar to Octreoscan at 24 h.

Deveci et al (Mol Imaging Radionucl Ther, 2013) assessed the diagnostic efficiency of ^{99m}Tc -EDDA/ HYNIC-Octreotate in comparison with ^{111}In pentetreotide scintigraphy in the detection of neuroendocrine tumours.

Altogether 14 patients were included and 36 of 40 lesions were shown with both ^{99m}Tc -EDDA/HYNIC-Octreotate, and ^{111}In -pentetreotide. However, 4 lesions were only visualized with ^{99m}Tc -EDDA/HYNIC-Octreotate.

In SPECT images, the tumor/liver, tumor/kidney, tumor/spleen, tumor/ background uptake ratios with ^{99m}Tc -EDDA/HYNIC-Octreotate were significantly higher than ^{111}In pentetreotide ratios ($p=0.015$, $p=0.007$, $p=0.025$ and $p=0.066$, respectively, Wilcoxon test).

The authors conclude that “ ^{99m}Tc -EDDA/HYNIC-Octreotate is a good alternative for SRS with the advantages of better pharmacokinetic properties, lower radiation dose and higher diagnostic accuracy especially when hybrid imaging methods (SPECT/CT) are used”.

This study was less well reported and “higher diagnostic accuracy” might be questioned, but in principle the results support prior findings.

A number of single arm studies have been reported, summarised here from the clinical overview:

Source	Malignancy	Patients	Sensitivity	Specificity	NPV	PPV	Accuracy
Chen L, 2009 ⁵²	Phaeochromocytoma	39	79.5%	96.6%	---	---	---
Gomez M, 2010 ⁵³	GEP-NET	32	87%	100%	---	---	---
Pavlovic S, 2010 ⁵⁴	NET	34	88%		---	---	---
Pusuwan P, 2010 ⁵⁵	Pancreatic NET	5	87%	100%	---	---	---
Nocun A, 2011 ⁵⁶	Large cell pulmonary NET	26	95.7%		---	---	---
Parisella MG, 2012 ⁵⁷	NET	50	70.3%	76.9%	---	---	72%
Sepúlveda-Méndez J, 2012 ⁵⁸	GEP-NET	56	88.4%	92.3%	70.6%	97.4%	89.3%
Artiko V, 2012 ⁵⁹	NET	30	87%	86%	67%	95%	87%

⁵² Chen L, Li F, Zhuang H, Jing H, Du Y, Zeng Z. 99mTc-HYNIC-TOC scintigraphy is superior to 131I-MIBG imaging in the evaluation of extraadrenal pheochromocytoma. *J Nucl Med.* 2009; 50:397-400.

⁵³ Gómez M, Ferrando R, Vilar J, Hitateguy R, López B, Moreira E, Kapitán M, De Lima F, Agüero B, Gabriela Villegas M, Urdaneta N, Gutiérrez E, Batteggazzore A, Bayardo K, Silveira A, Lago G, Páez A. 99mTc-octreotide in patients with neuroendocrine tumours from the GI tract. *Acta Gastroenterol Latinoam.* 2010; 40:332-8.

⁵⁴ Pavlovic S, Artiko V, Sobic-Saranovic D, Damjanovic S, Popovic B, Jakovic R, Petrasinovic Z, Jaksic E, Todorovic-Tirmanic M, Saranovic D, Micev M, Novosel S, Nikolic N, Obradovic V. The utility of 99mTc-HYNIC-TOC scintigraphy for assessment of lung lesions in patients with neuroendocrine tumours. *Neoplasma.* 2010; 57:68-73

⁵⁵ Pusuwan P, Tocharoenchai C, Sriussadaporn S, Muangsomboon K, Poromatikul N, Tiparaj R. Somatostatin Receptor Scintigraphy in Localization of Pancreatic Neuroendocrine tumours: A preliminary Study. *Siriraj Med J.* 2010; 63:53-56.

⁵⁶ Nocun A, Chrapko B., Gołębiewska R., Stefaniak B., Czekajska-Chehab E. Evaluation of somatostatin receptors in large cell pulmonary neuroendocrine carcinoma with 99mTc-HYNIC-TOC scintigraphy. *Nucl Med Commun.* 2011; 32:522-529.

⁵⁷ Parisella MG, Chianelli M, D'Alessandria C, Todino V, Mikolajczak R, Papini E, Dierckx RA, Scopinaro F, Signore A. Clinical indications to the use of 99mTc-HYNIC-TOC to detect somatostatin receptor-positive neuroendocrine tumours. *Q J Nucl Med Mol Imaging* 2012; 54:1-9.

⁵⁸ Sepúlveda-Méndez J, de Murphy CA, Pedraza-López M, Murphy-Stack E, Rojas-Bautista JC, González-Treviño O. Specificity and sensitivity of 99mTc-HYNIC-Tyr3-octreotide (99mTc-TOC) for imaging neuroendocrine tumours. *Nucl Med Commun.* 2012; 33:69-79.

A large number of tumours are known to express SSTR, especially small cell lung cancer, medullary thyroid cancer, Merkel cell carcinoma, neuroblastoma and pituitary adenoma, but also common tumours such as breast, colorectal, prostate and renal carcinoma may over express SSTR.

The table below is copied from ENETS “Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Somatostatin Receptor Imaging with ¹¹¹In-Pentetreotide (2009)”

It specifically discusses Octreoscan, but the paper is considered relevant also in this context.

Table 1. Sensitivity of SRI using pentetreotide

High sensitivity
Pituitary tumors [14]
GEPNET's
 Gastrinomas [15, 16]
 Nonfunctioning endocrine pancreatic tumors [17, 18]
 Functioning endocrine pancreatic tumors except
 insulinomas [17, 18]
 Carcinoids [19–22]
Parangliomas [23–25]
Small cell lung cancer [26–29]
Meningiomas [30, 31]
Sarcoidosis and other granulomatous diseases [12, 32]
Graves' disease and Graves' ophthalmopathy [33, 34]

Intermediate sensitivity
Insulinomas [17, 35]
Medullary thyroid carcinoma [36–38]
Differentiated thyroid carcinoma
 (including Hurthle cell carcinoma) [39–41]
Breast cancer [42]
Lymphoma (NHL, HL) [43, 44]
Pheochromocytoma [45]
Astrocytoma [31]

High sensitivity = Detection rate >75%; intermediate sensitivity = detection rate 40–75%. Sensitivity is either patient- or lesion-based. GEPNET = Gastroenteropancreatic neuroendocrine tumor; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma.

Data related to a study conducted in patients with medullary thyroid cancer are presented below. This is an uncommon disorder classified as NET. The results are as expected and the concordance between Octreoscan and Tektrotyd is reasonably high. Rafał Czepczyński et al Somatostatin receptor scintigraphy using ^{99m}Tc -EDDA/HYNIC-TOC in patients with medullary thyroid carcinoma.

Forty-five patients with MTC, aged 14–83 years, were investigated. Scintigraphy using ^{99m}Tc -EDDA/HYNIC-TOC (Tektrotyd) was performed 2 and 4 h post injection of 740 MBq (20 mCi) of the tracer. Other imaging techniques were also applied and analysed in individual cases (ultrasonography, computed tomography, ^{99m}Tc (V)-DMSA, ^{131}I -MIBG, ^{99m}Tc -MDP, ^{111}In -DTPA-octreotide and ^{18}F -FDG-PET) and compared with ^{99m}Tc -EDDA/ HYNIC-TOC.

As in previous studies, image acquisition was scheduled 2 and 4 h after tracer injection. Our data indicate that images obtained at both times are similar. However, in order to avoid misinterpretation of the images caused by artefacts or abdominal activity, we would recommend adherence to the dual acquisition regimen in routine practice.

Table 2 Comparison between ^{99m}Tc-EDDA/HYNIC-TOC and ¹¹¹In-DTPA-octreotide

Patient no. and group	^{99m} Tc-EDDA/HYNIC-TOC	¹¹¹ In-DTPA-octreotide
2, group 1	Thyroid tumour (TP)	Thyroid tumour (TP)
15, group 2	Thyroid tumour (TP)	Thyroid tumour (TP)
21, group 3	Mediastinal LN (TP)	Negative (FN)
24, group 3	Supraclavicular LN (TP)	Supraclavicular LN (TP)
28, group 3	Thyroid bed (TP)	Thyroid bed (TP)
30, group 3	Negative (FN)	Mediastinal LN (TP)
37, group 3	Thyroid bed (TP)	Benign lung nodule (FN)
38, group 3	Bone metastasis (TP)	Bone metastasis (TP)

TP true positive, *FN* false negative, *LN* lymph node

In group 1 (eight patients before thyroidectomy), uptake of the tracer was found in the primary tumours. In group 2 (six patients with remission), a false positive result was found in one patient; in the remaining five patients, no pathological foci were visualised. In group 3 (31 patients with post-surgical hyper-calcitoninaemia), scintigraphy was true positive in 23 patients (74.2%): uptake in the thyroid bed was found in five patients, in the lymph nodes in 18 and in bone metastases in four. Using ^{99m}Tc-EDDA/ HYNIC-TOC scintigraphy, the overall sensitivity was 79.5%, specificity 83.3%, accuracy 80.0%, positive predictive value 96.9% and negative predictive value 38.5%.

Authors' conclusions: ^{99m}Tc-EDDA/HYNIC-TOC is clinically useful for scintigraphy in the follow-up of patients with MTC. It can be used in clinical practice for preoperative evaluation, for localisation of local recurrence or distant metastases and particularly for therapy decision making.

It is agreed that Tektrotyd and Octreoscan could be of value, e.g. in the assessment of biochemical (calcitonin) recurrence of the disease.

A useful overview of the use of radio-imaging agents, including Tektrotyd, in NET is found in a paper by Valentina Ambrosini et al (Radiopeptide Imaging and Therapy in Europe, 2011). In this overview it is concluded that “^{99m}Tc-labeled somatostatin analogs have major advantages over ¹¹¹In-DTPA-octreotide such as better image quality, availability, price, and patient compliance; higher sensitivity and lower mean effective dose.”

There is a number of reports on the use of Tektrotyd in non-NET tumours, here illustrated with a study conducted in meningioma.

Wang et al. investigated the correlation between ^{99m}Tc-HYNIC-octreotide SPECT/CT somatostatin receptor scintigraphy and pathological grading and expression of sstr2 (J Neurooncol 2013).

All cases (30) of meningioma were positive on scanning and uptake correlated with tumour grade (see tables below).

Table 2 T/NT ratio of meningiomas of various pathological grades in SRS

Pathological grade	No. of cases	T/NT	90 % CI	P value
Grade I	20	3.80 ± 1.67	3.19–4.41	
Grade II	10	9.57 ± 3.78	7.61–11.53	0.001*

* Significant difference

(T=meningioma, TN=menigeal uptake contra lateral side)

The authors conclude that ^{99m}Tc-HYNIC-octreotide SPECT/CT SRS is a sensitive technique for the detection of meningioma, and the T/NT ratio of the SRS data closely correlates with the pathological grade of meningioma and the expression of SSTR2.

Also in non-malignant conditions, increased expression of SSTR has been described, e.g. sarcoidosis (or granulomatous conditions in general) and rheumatoid arthritis.

The expression of SSTR in sarcoidosis was found on the surface of epithelioid and giant cells, which form the sarcoid granuloma. In sarcoidosis patients, uptake of ¹¹¹In-pentetreotide decreased with successful corticosteroid therapy, suggesting that ¹¹¹In-pentetreotide binding reflected active sites of disease (Vanhagen PM, 1994; Kwekkeboom DJ, 1998).

Summary of Efficacy

A large number of also recently published studies support the use of Tektrotyd in the diagnosis and management of NET, only some of them discussed in this AR. Further studies are presented in the clinical overview. It cannot be concluded with certainty that Tektrotyd has superior diagnostic performance to Octreoscan, but it offers other advantages such as earlier imaging without loss of accuracy.

The proposed clinical indication reads:

- This medicinal product is for diagnostic use only. This is indicated for adults. For paediatric population see section 4.2. ^{99m}Tc-Tektrotyd specifically binds to somatostatin receptors.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the solution of ^{99m}Tc-Tektrotyd obtained is indicated for use as adjunct in the diagnosis and management of somatostatin receptor bearing gastro-entero-pancreatic neuroendocrine tumours (GEP-NET), by aiding their localization.

The preparation may be potentially useful in the case of other tumours expressing somatostatin receptors of various intensity.

Tumours which do not bear somatostatin receptors will not be visualised. In a number of patients suffering from GEP 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.”

There are no obvious reasons why the diagnostic value of Octreoscan and Tektrotyd should be different in NET in general provided that SSTR2 expression is similar. In this AR this is illustrated by the results obtained in medullary thyroid cancer. Therefore the RMS suggests that the restriction to NET of GEP origin should be removed.

The proposed indication further reads: “The preparation may be potentially useful in the case of other tumours expressing somatostatin receptors of various intensity.”

This is factually correct - “potentially useful” – and could even be expanded to some non-malignant conditions. Octreoscan, however, is a well-known diagnostic product since more than 10 years and the potential use of Octreoscan and Tektrotyd outside the key indication NET, should be left to the clinicians.

Proposed revised indication:

- 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 ~~gastro-entero-pancreatic~~-neuroendocrine tumours (GEP-NET), by aiding their localization.

~~The preparation may be potentially useful in the case of other tumours expressing somatostatin receptors of various intensity.~~

~~Tumours which do not bear somatostatin receptors will not be visualised. In a number of patients suffering from GEP 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.” (see section 4.4)~~

IV.4 Clinical safety

^{99m}Tc has a short physical half-life (about 6 h) and emits low energy radiation (141 keV).

In two studies using doses of about 740 to 1000 MBq the calculated effective dose was found to be about 3 to 6 mSv, i.e. about 6 mSv/1000 MBq (Gonzalez-Vazquez A, 2006 and Grimes J, 2011). This may be compared to ^{111}In -DTPA-octreotide, about 50 mSv/1000 MBq (IRCP 53/2008).

The average organ absorbed doses and effective dose of ^{99m}Tc -Tektrotyd administered to an adult patient [mGy/MBq]. (Grimes J, 2011)

Organ	Dose absorbed per one activity unit administered to a patient [mGy/MBq]
Adrenals	0.0060
Brain	0.0022
Breasts	0.0021
Gallbladder wall	0.0062
LLI wall	0.0038
Small intestine	0.0041
Stomach wall	0.0049
ULI wall	0.0042
Heart wall	0.0040
Kidneys	0.021
Liver	0.012
Lungs	0.0036
Muscle	0.0030
Ovaries	0.0042
Pancreas	0.0071
Red marrow	0.0030
Osteogenic cells	0.0079
Skin	0.0019
Spleen	0.030
Testes	0.0024
Thymus	0.0029
Thyroid	0.0040
Urinary bladder wall	0.014
Uterus	0.0045
Total body	0.0035
Effective dose (mSv/MBq)	0.0051

In the studies detailed in the clinical overview, doses between 200 and 925 MBq were used, most commonly around 740MBq. The activity to be administered for single photon emission tomography (SPECT) depends on the available equipment.

High quality SPECT images were obtained with 370 - 1020 MBq (in most cases 370 - 740 MBq) ^{99m}Tc -EDDA/HYNICTOC, therefore injection of 370 - 740 MBq ^{99m}Tc -Tektrotyd should be sufficient and can be recommended.

The administered doses are not different whether for SPECT or planar (Whole Body) imaging. As the effective dose is about 3.8 mSv when the 740 MBq ^{99m}Tc -Tektrotyd is administered, the adverse events related to ionising radiation are expected to occur with a very low probability. To contextualise, an effective dose of 1 – 10 mSv is considered a very low risk radiation dose, increasing the risk of dying from cancer of about 1 - 10 per 20,000 individuals over a life-time.

The precautionary measures implemented in the SPC are considered adequate.

Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/ Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the Summary is considered acceptable.

IV.5 Risk Management Plans

The MAH has submitted a risk management plan in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tektrotyd.

Summary table of safety concerns as proposed by the Applicant in the RMP

Summary of safety concerns	
Important identified risks	Carcinogenity and hereditary effects due to radiation exposure
Important potential risks	Hypersensitivity reactions
	Rebound effects in case of withdrawal of therapy with somatostatin analogues
	Inhibition of glucagon secretion

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures SmPC	Other routine risk minimisation measures	Additional risk minimisation measures
Carcinogenity and hereditary effects	Text in section 4.2 Warning in section 4.4 Listed in section 4.8 General Warning in section 6.6	<ul style="list-style-type: none"> • Prescription only medicine • Radiopharmaceuticals may only be used by trained and qualified personnel with an appropriate government authorization for the use and handling of radionuclides 	---
Hypersensitivity reactions	Warning in section 4.3 Warning in section 4.4	<ul style="list-style-type: none"> • Use restricted to physicians and medical personnel trained and qualified in the use of radiopharmaceuticals • Use always in presence of nuclear physician, who is able to take necessary actions in case of 	---

Safety concern	Routine risk minimisation measures SmPC	Other routine risk minimisation measures	Additional risk minimisation measures
		emergency	
Rebound effects in case of withdrawal of therapy with somatostatin analogues	Warning in section 4.4 Warning in section 4.5	<ul style="list-style-type: none"> • Prescription only medicine • Use always in presence of nuclear physician, observing and preventing the occurrence of potential interactions 	---
Inhibition of glucagon secretion	Warning in section 4.4	<ul style="list-style-type: none"> • Prescription only medicine • Use always in presence of nuclear physician, observing and possibly recommending more frequent monitoring of glucose level 	---

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

The RMP is approvable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

The MAH shall submit the first periodic safety update report for this product within 12 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Polish.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This is a well-established use application for a medicinal product for diagnostic use only with the proposed indication focused on gastro-entero-pancreatic neuroendocrine tumours (GEP-NET), i.e. the indication for the use of Octreoscan, licensed for more than 15 years.

The main difference from Octreoscan is that ^{99m}Tc is used instead of ^{111}In . Tektrotyd is licensed in Poland and a large number of published papers have been submitted in support of the application, the most recent from 2015. Therefore the criteria for “well established use” are considered to be fulfilled.

Benefit

The reported sensitivity and specificity varies in relation to the NET expression of somatostatin receptors (SSTR), mainly SSTR2, but has been reported to be about 80 and 90%. Compared with Octreoscan at least similar diagnostic performance has been demonstrated. In addition scanning may be performed after (1-2h and) 4 hours instead of after about 24 hours as for Octreoscan without loss in diagnostic accuracy.

Risk

The recommended dose of Tektrotyd is 370 to 740 MBq and the effective dose is about 3.8 mSv when 740 MBq ^{99m}Tc -Tektrotyd has administered. This means that the effective dose is lower than after Octreoscan.

To contextualise, an effective dose of 1 – 10 mSv is considered a very low risk radiation dose, increasing the risk of dying from cancer of about 1 - 10 per 20,000 individuals over a life-time.

Transient headache or epigastric pain may occur directly after administration of ^{99m}Tc -Tektrotyd.

Based on a request from Hungary the following wording has been included in section 4.4 of the SPC:

“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 analogues.”

The normal starting dose of Octreotide is 50 microg x 1-2 and the dose of Tektrotyd is 20 micrograms as a single dose. The likelihood of a relevant pharmacodynamic effect is considered very low, but the MAH and the RMS have accepted the wording for inclusion.

Discussion of Benefit – Risk

The revised wording of the indication:

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”).

is supported by submitted data.

Benefit – Risk

From a clinical perspective benefit – risk is considered favourable for Tektrotyd.

The quality of the product is found adequate. There are no objections to approval of Tektrotyd, from a non-clinical and clinical point of view. The product information is acceptable.

The application is recommended for approval.

VII. APPROVAL

The Decentralised procedure for Tektrotyd, 20 micrograms, kit for radiopharmaceutical preparation was positively finalised on 2016-05-24.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)