OCTREO RPHPHARMA

PLEASE READ CAREFULLY BEFORE USING THE PRODUCT.

DRUG FOR DIAGNOSTIC USE IN NUCLEAR MEDICINE.
This product is only for use in specialized clinics and hospitals.

PHARMACEUTICAL FORM AND PRESENTATION
Kit containing 1 vial (A) of lyophilized reagent and 1 vial (B) of 0.2M buffer solution, sterile and pyrogen-free, sealed under nitrogen atmosphere.

COMPOSITION
Each kit contains the following products:

Composition	
Vial A	**Amount**
hydrazinonicotinamide-Tyr3-octreotide (HYNIC-TOC)	20.0 µg
stannous chloride dihydrate	20.0 µg
ethylenediamine N, N'-diacetic acid (EDDA)	10.0 mg
tricine	20.0 mg
mannitol	50.0 mg
ascorbic acid	0.01 mg
Composition	
Vial B	**Amount**
anhydrous dibasic sodium phosphate	56.6 mg
water for injection QS	2.0 mL

Table 1 – Composition of the OCTREO kit vials

1. INDICATIONS
The radiopharmaceutical OCTREO-Tc-99m is recommended for the diagnostic imaging of tumors that express somatostatin receptors, especially those of neuroendocrine origin.

INTRAVENOUS ADMINISTRATION. ADULT AND PEDIATRIC USE.

2. EFFICACY
OCTREO-Tc-99m efficacy on neuroendocrine tumors detection was performed by several studies (Decristoforo *et al*, 2000 b; Bangard et al., 2000). These studies showed OCTREO-Tc-99m is diagnostically greater than Octreoscan-In-111 (Hubalewska-Dydejczyk *et al*., 2006). Some kinds of lung tumors express neuroendocrine receptors. For these tumors, OCTREO-Tc-99m was an important diagnostic tool.

3. PHARMACOLOGICAL CHARACTERISTICS
The radiopharmaceutical OCTREO-Tc-99m is a multifunctional peptide analogue of somatostatin synthesized by the neuroendocrine system and other cells present in different tissues and organs. Somatostatin receptors are expressed by many neuroendocrine tumors as well as organs like the liver, spleen, pituitary gland, thyroid and kidneys. Other organs can also be observed because of the radiopharmaceutical excretion, as bladder and urethras. It is quickly cleared from the bloodstream: 35% of injected activity remains in the bloodstream within 10 minutes and only 1% remains after 20 hours administration. It is predominantly eliminated through the kidneys: approximately 50% is found in the urine within 6 hours and 85% in the first 24 hours. Gastrointestinal clearance accounts for only 2% of the total injected activity.

4. CONTRAINDICATIONS
There are no reported contraindications.

5. WARNINGS AND PRECAUTIONS
During pregnancy or breastfeeding, this radiopharmaceutical should only be used in cases of extreme necessity, when the risk of exposure of the fetus or newborn to radiation is justified by the importance of diagnosis.
The administration of a radiopharmaceutical during pregnancy can cause mutagenic changes in the fetus.
During lactation, technetium-99m (99m Tc) is excreted in breast milk. Breastfeeding should be suspended for at least 12 hours after injection and the milk produced during this period discarded.
Avoid close contact between mother and baby for the 12 hours following administration of the radiopharmaceutical.

6. DRUG INTERACTIONS INTERACTIONS
Simultaneous administration of somatostatin analogues may result in false negatives due to competition for the receptor site.

7. STORAGE PRECAUTIONS
Date of manufacture and expiry: see packaging.
Transport at room temperature and store in a cool dark place at temperatures between 2 and 8° C.
When added to the vial of OCTREO without the presence of air, the sterile pyrogen-free solution of sodium pertechnetate (Na 99mTcO_4) produces rapid labeling that remains stable *in vitro* for 4 hours.

After complexation with technetium-99m (99m Tc) store in the dark between 2° and 30° C.

Lot number, manufacture and expiration dates: see packaging.
Do not take medication that has expired.
All medication should be kept out of reach of children.
Before administering to the patient, take note of the appearance of the product, which should be clear and colorless.

8. DOSAGE AND USE INSTRUCTIONS
Route of administration: intravenous.
The recommended dose for tumor scintigraphy in adults weighing 70 Kg is 370 MBq (10 mCi) to 555 MBq (15 mCi). For pediatric patients the dose should be adjusted according to age, weight and body mass index.

8.1. INSTRUCTIONS FOR PREPARATION AND STORAGE AFTER COMPLEXATION
Use aseptic procedures and take precautions to prevent exposure to radiation.
- Remove the reagent kit from refrigeration and wait until it reaches room temperature.
- Remove the plastic caps and aseptically sterilize the upper sections using 70% ethyl alcohol.
- Switch on the water bath and wait until the temperature reaches 100°C.
- Correctly and carefully place vial A inside the lead shield.
- Add 1mL of the sterile solution in vial B to the lyophilized powder in vial A, preventing air from entering the vials.
- Without removing the needle, aspirate an equal volume of air to maintain atmospheric pressure within the bottle.
- Gentle swirl vial A until its contents have dissolved completely.
- Add 1 to 2 mL of a sterile, pyrogen and oxidant-free solution of Na - 99mTcO4 (maximum 30 mCi), recently eluted from a generator (less than 1 hour), with an inter-elution period no greater than 24 hours. **DO NOT USE THE FIRST ELUATE FROM NEW GENERATORS.**
- Mix gently and incubate for 10 minutes in a water bath at 100°C. After incubation remove the vial from the water bath and let cool at room temperature inside a lead shield for 5 minutes.
- Label the vial with the following information: name of the radiopharmaceutical, total activity, radioactive content and labeling time.
- Before administration, check the appearance, pH and radiochemical purity.
- Next, extract doses in accordance with the patient's body weight, taking care to avoid the entry of air when handling the flask.

8.2. QUALITY CONTROL - RADIOCHEMICAL
Use three silica gel 60 plates measuring 6.5 cm long and 1 cm wide, as shown in figure 1. Once the complexation incubation time has elapsed, add a drop of the material on the application line of each of the plates. Place Plate 1 in a chromatographic tank containing Butanone PA, PLATE 2 in a chromatographic tank containing a solution of methanol/1 M ammonium acetate (1: 1) and PLATE 3 in an chromatographic tank containing a 0.1M sodium citrate solution. Wait until the solvents migrate to the top lines of the respective plates, which can happen at different times. Remove the plates from the chromatography tanks. Cut plates 1 and 3 in half. Cut plate 2 1.5 cm from the application point. Calculate labeling efficiency using the formula below. Analyze the results of labeling efficiency in accordance with table 2.

NOTE: The solutions of 1M ammonium acetate and 0.1 M sodium citrate must be prepared with distilled water.

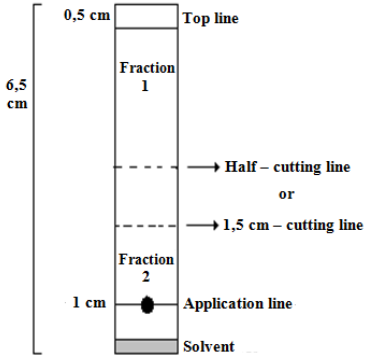

Figure 1 – Cutting the chromatography plates

Labeling efficiency (%) =

100 – (% 99mTcO_4^- + % 99mTcO_2 + % 99mTc-coligand), where:

Plate 1:
% 99mTcO_4^-:

$$\frac{\text{activ. Fraction 1}}{\text{activ. Fraction 1+2}} \times 100 \leq 5\%$$

Plate 2:
% 99mTcO_2:

$$\frac{\text{activ. Fraction 2}}{\text{activ. Fraction 1+2}} \times 100 \leq 5\%$$

Plate 3:
% (99mTc-coligand + % 99mTcO_4^-):

$$\frac{\text{activ. Fraction 1}}{\text{activ. Fraction 1+2}} \times 100 \leq 10\%$$

NOTE: % 99mTc-coligand = % (99mTc-coligand + % $99mTcO_4^-$) – % $99mTcO_4^-$

Labeling efficiency should be greater than or equal to 80%.

Chromatography Analysis of OCTREO-Tc-99m			
Chromatography System		**(99m Tc) Species**	
Stationary Phase	**Mobile Phase**	**Origin**	**Front**
Plate 1 (Silica gel 60)	Butanone PA	OCTREO-Tc-99m $99mTcO_2$, 99mTc-coligand	$99mTcO_4^-$
Plate 2 (Silica gel 60)	Methanol/1M Ammonium Acetate (1:1)	$99mTcO_2$	99m-Tc-OCTREO $99mTcO_4^-$, 99mTc-coligand
Plate 3 (Silica gel 60)	0.1M sodium citrate	OCTREO-Tc-99m, 99mTc-coligand	99mTc-coligand, $99mTcO_4^-$

Table 2 – Chromatography systems for radiochemical control of OCTREO-Tc-99m.

8.3. QUALITY CONTROL - pH

Apply a sample of the radiopharmaceutical on the pH indicator strip. Wait 30 seconds and compare the strip color with the parameters in this box.
The pH range for the radiopharmaceutical OCTREO-Tc-99m should be between 5.0 and 7.0.

8.4. PRECAUTIONS ON ADMINISTRATION

This drug becomes radioactive after adding sodium pertechnetate solution. The use of lead shielding, suitable gloves and goggles should be mandatory.
The components of the kits are sterile and pyrogen-free. In order to preserve the sterility of the product, it should be handled in accordance with the Good Practices on Handling Sterile Products (intravenous products).
Precautions should be taken when using ionizing radiation. As such, radioactive waste (used materials, recipients and other waste) should be correctly disposed of in compliance with radiation protection guidelines.

DOSES ADMINISTERED TO CHILDREN AND ELDERLY SHOULD BE CALCULATED ACCORDING TO THE BODY SURFACE AREA

8.5. TOXICITY TESTS

Toxicity is not an issue when considering the design and development of radiopharmaceuticals due to the small amount used, which does not produce a pharmacological response.

8.6. PHYSICAL CHARACTERISTICS OF METASTABLE TECHNETIUM-99M

Tecnetium-99m (99m Tc) has the ideal physical properties for studying scintigraphic images.
(99m Tc) decreases into technetium-99 through isomeric transition and has a physical half-life of 6.02 hours.

RADIATION	AVERAGE/DECAY (5)	AVERAGE ENERGY (keV)
Gama -2	89.07	140.5

Table 3 – Data on the main radiation emitted
'Kocher, David C., "Radioactive Decay Data Tables," DOE/ TIC-11026. 108(1981).

8.7. DOSAGE

The dose absorbed by a 70 Kg patient on administration of OCTREO-Tc-99m is shown in table 4:

Organ	mSv/MBq
Kidneys	0.0288
Liver	0.00745
Spleen	0.0325
Intestine	0.0105
Lungs	0.00167
Bone marrow	0.00143
Muscles	0.00114
Ovaries	0.00242
Testicles	0.000426
Effective dose	**0.0060**

Table 4 – Dosage for administering OCTREO-Tc-99m. Source: González-Vázquez et al., 2006.

8.8. EXTERNAL RADIATION

The constant dose for technetium-99m (99m Tc) is 0.78 R/mCi*h at 1 cm. The first half-value layer is 0.017 cm of lead (Pb). Attenuation resulting from various thicknesses of lead is described in table 5.

SHIELD THICKNESS (Pb) cm	COEFFICIENT OF ATTENUATION
0.017	0.5
0.08	0.1
0.15	0.01
0.25	0.001
0.33	0.0001

Table 5 – Radiation attenuation by lead shielding.

Table 6 shows the correction for the physical decline of technetium-99m, after calibration time.

HOUR	REMAINING FRACTION	HOUR	REMAINING FRACTION
1	0.891	7	0.447
2	0.794	8	0.398
3	0.708	9	0.355
4	0.631	10	0.316
5	0.562	11	0.282
6	0.501	12	0.251

Table 6 – Physical decline; half-life of technetium-99m (99m Tc): 6.02 hours.

9. SIDE EFFECTS

There are no reports of side effects.

10. OVERDOSE

In case of a radiation overdose with OCTREO-Tc-99m the patient's absorbed dose should be lowered as much as possible by ingesting more liquids to eliminate the radionuclide from the body through an increase of urination.

In case of poisoning call 0800 722 6001 for instructions of how to proceed.

RESPONSIBLE PHARMACIST
Manoela Michelon Grazziotin
CRF/RS: 10225

GRUPORPH
Avenida Ipiranga, 6681 – Prédio 93 – Sala 101
TECNOPUC – Porto Alegre – RS – 90619-900
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MJM PRODUTOS FARMACÊUTICOS E DE RADIOPROTEÇÃO LTDA
CNPJ: 04.891.262/0001-44

CUSTOMER SERVICE
Phone/Fax:+55 (51) 3336.7134