PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# OCTREOSCAN™

Kit for the preparation of Indium In 111 Pentetreotide

Powder for Solution & Solution, 3 mCi/mL, Intravenous

Radiodiagnostic Agent V09IB01

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**RECENT MAJOR LABEL CHANGES**

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**Sections or subsections that are not applicable at the time of authorization are not listed .**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

OCTREOSCAN ™, Kit for the preparation of Indium In 111 pentetreotide, is a diagnostic radiopharmaceutical (schedule C) and is indicated:

- As an adjunct agent for the scintigraphic localization of primary and metastatic neuroendocrine tumours bearing somatostatin receptors.

### 1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

### 1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

## 2 CONTRAINDICATIONS

Not known.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

| **Serious Warnings and Precautions** |
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| Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans. |

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

- Refer to Section 7 WARNINGS AND PRECAUTIONS.
- Before administration, the patient should be well hydrated.
- After administration, the patient must be encouraged to drink fluids liberally. Elimination of extra fluid intake will help reduce the radiation dose by flushing out unbound, labelled pentetreotide by glomerular filtration.
- It is also recommended that a mild laxative (e.g., bisacodyl or lactulose) be given to the patient starting the evening before the radioactive drug is administered, and continuing for 48 hours. Ample fluid uptake is necessary during this period as a support both to renal elimination and the bowel-cleansing process.
- In a patient with an insulinoma, bowel-cleansing should be undertaken only after consultation with an endocrinologist.

### 4.2 Recommended Dose and Dosage Adjustment

- Health Canada has not authorized an indication for pediatric or geriatric use.
- No dosage adjustment required in hepatic or renal impairment.
- The recommended intravenous dose for Planar imaging is 111 MBq (3.0 mCi) of Indium In 111 pentetreotide prepared from an Octreoscan kit.
- The recommended intravenous dose for SPECT imaging is 222 MBq (6.0 mCi) of Indium In 111 pentetreotide prepared from an Octreoscan kit.

### 4.3 Reconstitution

**Parenteral Products**:

- Indium In 111 pentetreotide is prepared by combining the two kit components (Refer to Section 4.7: Instruction for Preparation and Use). Indium In 111 reacts with the diethylenetriaminetetra- acetic acid portion of the pentetreotide molecule to form Indium In 111 pentetreotide. The pH of the resultant Indium In 111 pentetreotide solution is between 3.8 and 4.3. No bacteriostatic preservative is present.
- The Indium In 111 pentetreotide solution is suitable for intravenous administration as is, or it may be diluted to a maximum volume of 3.0 mL with 0.9% Sodium Chloride Injection, USP, immediately before intravenous administration. In either case, the labelling yield of Indium In 111 pentetreotide should be determined before administration to the patient. A method recommended for determining the labelling yield is presented in Section 4.4 Administration.
- The Octreoscan Kit should be stored at **2°C to 8°C**.
- Indium In 111 Chloride Sterile Solution is stable up to 10 days after the end of bombardment.
- An expiration date of two years has been established for the Octreoscan Reaction Vial. Do not use the kit beyond the expiration date stamped on the box.
- After reconstitution, store at controlled room temperature (20°C to 25°C).
- Remaining product or components should be disposed of in a safe manner, in compliance with applicable regulations. Refer to Section 11: STORAGE, STABILITY AND DISPOSAL.

**Table 1 - Reconstitution.**

| Vial Size | Volume of Diluent to be Added to Vial | Approximate Available Volume | Concentration per mL |
|---|---|---|---|
| 10 mL | 1 mL | 1.1 mL | 3.0 mCi/mL Indium In 111 pentetreotide |

### 4.4 Administration

The recommended time for Planar and SPECT imaging is 4 hours and 24 hours. A follow-up image may be taken at 48 hours, if indicated.

The patient dose should be confirmed by a suitably calibrated radioactivity ionization chamber immediately before administration.

The radiochemical purity of the reconstituted solution must be checked prior to administration to the

patient. See below for the recommended method and the alternate method.

**Recommended Method For Determination Of Labelling Yield Of Indium In 111 Pentetreotide:**

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| Required Materials<br><br>*Sep-Pak™ is a trademark of Waters Technologies Corporation. | • Waters (Division of Millipore) Sep-Pak™ C18 Cartridge, Part No. 51910*.<br>• Methanol, 15 mL (**Caution:** toxic and flammable. Exercise due caution).<br>• Distilled water, 20 mL.<br>• Disposable syringes: 2 x 10 mL, no needle required<br>2 x 5 mL, no needle required<br>1 x 1 mL, with needle<br>• Three disposable culture tubes or vials, minimum 10-mL capacity.<br>• Ion Chamber. |
| Preparation of the Sep-Pak Cartridge | 1. Rinse the Sep-Pak cartridge with 10 mL of methanol as follows: fill a 10-mL syringe with 10 mL of methanol; attach the syringe to the longer end of the Sep-Pak cartridge; and push the methanol through the cartridge. Discard the eluate in a safe and approved manner.<br>2. Similarly, rinse the cartridge with 10 mL of water. Ensure that the cartridge is kept wet and that there is no air bubble present. If an air bubble is present, rinse the cartridge with an additional 5 mL of water. Discard the eluate. |
| Sample Analysis | 3. Using a 1-mL syringe with needle, withdraw 0.05 - 0.1 mL Indium In 111 pentetreotide from the Octreoscan Reaction Vial. Apply the preparation to the Sep-Pak cartridge through the longer end of the cartridge. Make sure that the sample is migrating onto the column of the cartridge.<br>4. **NOTE: AFTER THIS STEP, THE CARTRIDGE AND ALL SOLUTIONS ELUTED FROM IT WILL BE RADIOACTIVE.**<br>5. With a disposable 5-mL syringe, slowly (in dropwise manner) push 5 mL of water through the longer end of the cartridge, collecting the eluate in a counting vial or tube. Label this eluate as "Fraction 1".<br>6. Similarly, elute the cartridge with 5 mL of methanol. Be sure that this solution is pushed slowly through the longer end of the cartridge so that the elution occurs in a dropwise manner. Collect this fraction in a second culture tube or vial for counting. Label it as "Fraction 2". Push two 5-mL portions of air through the longer end of the cartridge and collect the eluate with "Fraction 2".<br>7. Place the Sep-Pak cartridge in a third culture tube or vial for assay. |
| Assay | 8. Assay the activity of "Fraction 1" in a suitably calibrated ionization chamber. This fraction contains the hydrophilic impurities (e.g., unbound Indium In 111).<br>9. Assay the activity of "Fraction 2". This fraction contains the Indium In 111 pentetreotide.<br>10. Assay the activity of the Sep-Pak cartridge. This component contains the remaining non-elutable impurities.<br>11. Dispose of all of the materials used in the preparation, the sample |

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| | analysis, and the assay in a safe and approved manner. |
| Calculations | 12. % Indium In 111 pentetreotide = "Fraction 2" Activity / Total Activity X 100%<br>Where Total Activity = "Fraction 1" + "Fraction 2" + Activity remaining in Sep-Pak.<br><br>**NOTE: IF THIS VALUE IS LESS THAN 90%, DO NOT USE THE PREPARATION. DISCARD IT IN A SAFE AND APPROVED MANNER.**<br><br>13. % hydrophilic impurities = "Fraction 1" Activity / Total Activity X 100%<br><br>14. % non-elutable impurities = Activity remaining in Sep-Pak / Total Activity X 100% |

**Alternate Method For Determination Of Labelling Yield Of Indium In 111 Pentetreotide:**

Analysis of Indium In 111-bound peptides versus Indium In 111-bound non-peptide compounds may be done on silicagel impregnated glass fiber strips (ITLC SG by Gelman, cat.no. 61885). Prepare a thoroughly dried strip approximately 10 cm long and 2.5 cm wide by marking a starting line at 2 cm, with additional marks at 6 and 9 cm. Apply 5 to 10 µLof the reconstituted and labeled solution to the starting line and develop in freshly prepared sodium citrate solution 0.1 N, adjusted with HCl to pH 5. In approximately 2-3 min, the front will have reached the 9 cm mark. Cut the strip at the 6 cm mark and measure the activity of both halves. Non-peptide bound Indium In 111 moves with the front.

Requirement: The lower end of the chromatogram should contain ≥ 90% of the applied activity.

**Patient Preparation:**

- **Bowel preparation:** Administer a mild laxative (e.g., bisacodyl or lactulose) before and after Indium In 111 pentetreotide injection to minimize potential for visualizing artifacts in the intestine.
- **Hydration**: Patients should be well hydrated (at least 2 glasses of water) to enhance renal clearance.
- **Concurrent octreotide therapy:** Discontinue 24 to 48 hours prior to imaging (if possible) and monitor patient for signs of octreotide withdrawal.

### 4.5 Missed Dose

Not applicable

### 4.6 Image Acquisition and Interpretation

**Planar Imaging Protocol**: Planar imaging is preferably performed at 24 hours post-injection. Abdominal lesions with a low density may be missed at 4 hours which become visible at 24 hours due to the lower background activity. Abdominal imaging may be repeated at 48 hours if needed to differentiate between tumour and normal bowel uptake. If relatively short count times are encountered (due to high activity

locations within the field of view) additional views with longer count times should be considered in order to effectively visualize lesions with a lower somatostatin receptor density.

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| Camera settings | • LFOV gamma camera with medium-energy parallel-hole collimator.<br>• 20% windows centered over both Indium In 111 peaks (172 KeV and 245 KeV).<br>• Data from both windows should be added to acquisition frames. |
| Image acquisition<br><br>(all planar images) | • Anterior and posterior views.<br>• 128 x 128 word matrix. |
| Head and neck imaging | Preset 300,000 counts (10 min preset imaging time) at 24 hours. |
| Chest imaging | • Preset 500,000 counts (10 min preset time) at 24 hours.<br>• Include only small upper rim of the liver and spleen.<br>• Projections of shoulders with upraised arms (when axillary metastases are suspected). |
| Abdominal imaging | • Preset 500,000 counts (10 min preset time) at 24 hours.<br>• Preset 500,000 counts (~ 10 min preset time) at 48 hours.<br>• Upper abdomen (including liver, spleen, and kidneys).<br>• Lower abdomen (including lower rim of both kidneys). |
| Whole body imaging | Minimum 30-min count time from head through pelvis at 24 and 48 hours. |

**SPECT Imaging Protocol:** SPECT imaging is recommended at 24 hours post-injection for small tumours poorly visualized by planar imaging due to over-projection by other tissues and organs. SPECT imaging often provides better anatomical delineation of tumour location, particularly when planar imaging shows homogeneous uptake, such as cases involving liver metastases. Abdominal SPECT usually is necessary unless metastases have been confirmed previously.

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| Camera settings | • LFOV gamma camera with medium-energy parallel-hole collimator.<br>• 20% windows centered over both Indium In 111 peaks (172 KeV and 245 KeV).<br>• Data from both windows are added to acquisition frames. |
| SPECT acquisition<br>(single-head camera) | • 60 projections.<br>• 45 - 60 s per step.<br>• 64 x 64 word matrix (or higher).<br>• 360° rotation. |
| SPECT acquisition<br>(triple-head camera) | • 120 projections.<br>• 30 s per step. |

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| | • 64 x 64 word matrix (or higher).<br>• 360° rotation. |
| SPECT analysis | • 1-pixel slice width.<br>• Pre-filter (Wiener, or other comparable filter) applied to original data.<br>• Filtered data reconstruction with a Ramp (or other comparable filter). |

### 4.7 Instructions for Preparation and Use

**Note**: Read complete directions thoroughly before starting preparation procedure.

**Procedural Precautions And Notes:**

- The components are sterile and non-pyrogenic. Use aseptic technique and wear waterproof gloves throughout the entire preparation procedure, and while withdrawing the patient-dose from the Octreoscan Reaction Vial.
- Make all transfers of radioactive Indium In 111 Chloride Sterile Solution to the Octreoscan Reaction Vial with an adequately shielded sterile syringe and maintain adequate shielding around the Indium In 111 pentetreotide vial during the useful life of the radioactivity. Use the transfer needle provided in the kit.
- DO NOT inject into TPN (total parenteral nutrition) administration bags or their intravenous lines.

**Procedure For The Preparation of Indium In 111 Pentetreotide:**

- Place the Octreoscan Reaction Vial in a lead dispensing shield (of minimum wall thickness 3 mm) fitted with a lid.
- Swab the rubber stopper of the Reaction Vial with an appropriate antiseptic and allow the vial to dry.
- Aseptically remove the contents of the Indium In 111 Chloride Sterile Solution vial using the needle provided and a shielded, sterile syringe.
- Inject the Indium In 111 Chloride Sterile Solution into the Octreoscan Reaction Vial.
- Gently swirl the Octreoscan Reaction Vial until the lyophilized pellet is completely dissolved.
- Incubate the Indium In 111 pentetreotide solution at or below 25°C for a minimum of 30 min. **Note: A 30-min incubation time is required. Shorter incubation periods may result in inadequate labelling.**
- Using proper shielding, visually inspect the vial contents. The solution should be clear, colourless and free of particulate matter. If not, the preparation should not be used. It should be disposed of in a safe and approved manner.
- Assay the Indium In 111 pentetreotide solution using a suitably calibrated ionization chamber. Record the date, time, total activity, and patient identifier (e.g., patient name and number) on the radioassay information label and affix the label to the lead dispensing shield.
- **The labelling yield of the reconstituted solution must be checked before administration to the patient, according to the instructions given below. If the radiochemical purity is < 90%, the product should not be used.** Refer to Section 4.4.

- Store the Reaction Vial containing the Indium In 111 pentetreotide solution at controlled room temperature (20°C to 25°C) until use. **The Indium In 111 pentetreotide must be used within six hours of preparation.**
- If desired, the preparation can be diluted to a maximum volume of 3 mL with 0.9% Sodium Chloride Injection, USP immediately prior to injection. The sample should be drawn up into a shielded, sterile syringe and administered to the patient.

### 4.8 Radiation Dosimetry

The estimated radiation doses (Values listed include a correction for a maximum of 0.1% Indium In 114m radiocontaminant at calibration) to the average adult (70 kg) from intravenous administration of Indium In 111 pentetreotide are presented in Table 2. These estimates were calculated by Oak Ridge Associated Universities using the data published by Krenning, et al. (E.P. Krenning, W.H. Bakker, P.P.M. Kooij, W.A.P. Breeman, H.Y. Oei, M. de Jong, J.C. Reubi, T.J. Visser, C. Bruns, D.J. Kwekkeboom, A.E.M. Reijs, P.M. van Hagen, J.W. Koper and S.W.J. Lamberts, "Somatostatin Receptor Scintigraphy with Indium-111-DTPA-D- Phe-1-Octreotide in Man: Metabolism, Dosimetry and Comparison with Iodine-123-Tyr-3-Octreotide," *The Journal of Nuclear Medicine*, Vol. 33, NO. 5, May 1992, pp. 652-658).

**Table 2: Final Dose Estimates: Estimated Absorbed Radiation Doses After Intravenous Administration of Indium In 111 Pentetreotide to a 70 kg Patient** (Assumes 4.8 hour voiding interval and International Commission on Radiological Protection (ICRP) 30 model for the gastrointestinal tract calculations).

| ORGAN | mGy/MBq | rad/mCi |
|---|---|---|
| Adrenals | 0.06 | 0.22 |
| Brain | 0.014 | 0.051 |
| Breasts | 0.014 | 0.051 |
| Gallbladder Wall | 0.053 | 0.20 |
| LLI Wall | 0.084 | 0.31 |
| Small Intestine | 0.044 | 0.16 |
| Stomach | 0.041 | 0.15 |
| ULI Wall | 0.056 | 0.21 |
| Heart Wall | 0.026 | 0.096 |
| Kidneys | 0.52 | 1.9 |
| Liver | 0.065 | 0.24 |
| Lungs | 0.023 | 0.085 |
| Muscle | 0.026 | 0.097 |
| Ovaries | 0.047 | 0.17 |
| Pancreas | 0.063 | 0.23 |
| Red Marrow | 0.029 | 0.11 |
| Bone Surfaces | 0.035 | 0.13 |
| Skin | 0.014 | 0.053 |
| Spleen | 0.034 | 1.3 |
| Testes | 0.027 | 0.10 |
| Thymus | 0.018 | 0.068 |
| Thyroid | 0.17 | 0.063 |
| Urinary Bladder | 0.35 | 1.3 |
| Uterus | 0.065 | 0.24 |
| Total Body | 0.030 | 0.11 |

| ORGAN | mGy/MBq | rad/mCi |
|---|---|---|
| Effective Dose Equivalent<br>Estimated according to ICRP Publication 53 | 0.10 mSv/MBq | 0.38 rem/mCi |

## 5 OVERDOSAGE

In the event of a radiation overdose, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body using reinforced hydration and frequent bladder voiding. A diuretic might also be considered. If possible, an estimate of the radioactive dose given to the patient should be performed. For management of a suspected drug overdose, contact your regional poison control center.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

The Octreoscan, kit for the preparation of Indium In 111 pentetreotide, is a diagnostic radiopharmaceutical kit consisting of two components as described in the table below:

**Table 3 – Dosage Forms, Strengths, Composition and Packaging.**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Intravenous | 10-mL Octreoscan Reaction Vial containing 10 µg pentetreotide | 0.37 mg citric acid, anhydrous;<br>2.0 mg gentisic acid [2,5-dihydroxybenzoic acid];<br>10.0 mg inositol;<br>4.9 mg trisodium citrate, anhydrous. |
| | 10-mL vial of Indium In 111 Chloride Sterile Solution containing 1.1 mL of 111 MBq/mL (3.0 mCi/mL) Indium In 111 chloride (at time of calibration) | 3.5 µg/mL (ferric ion, 1.2 µg/mL);<br>0.02 N HCl. |

Prior to lyophilization, sodium hydroxide or hydrochloric acid may have been added for pH adjustment. The vial contents are sterile and non-pyrogenic. No bacteriostatic preservative is present.

In addition, the kit also contains the following items: a 25 G x 5/8" needle (BD, Monoject) used to transfer Indium In 111 Chloride Sterile Solution to the Octreoscan Reaction Vial, pressure sensitive label, and a package insert.

### 6.1 Physical Characteristics

Per the Radiopharmaceutical Internal Dosimetry Information Center, Oak Ridge Associated Universities, Oak Ridge, TN 37831-0117, February 1985, Indium In 111 decays by electron capture to cadmium Cd 111

(stable) and has a physical half-life of 2.805 days (67.32 hours). The principal photons that are useful for detection and imaging are listed in Table 4.

**Table 4. Principal Radiation Emission Data** per Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC-11026, 115 (1981).

| RADIATION | MEAN PERCENT/ DISINTEGRATION | ENERGY (keV) |
|---|---|---|
| Gamma-2 | 90.2 | 171.3 |
| Gamma-3 | 94.0 | 245.4 |

Table 5 lists the fractions remaining at selected time intervals before and after calibration. This information may be used to correct for physical decay of the radionuclide.

**Table 5. Physical Decay Chart: Indium In 111, Half-life 2.805 days (67.32 hours).**

| Hours | Fraction Remaining | Hours | Fraction Remaining |
|---|---|---|---|
| -72 | 2.100 | 0* | 1.000 |
| -60 | 1.854 | 3 | 0.970 |
| -48 | 1.639 | 6 | 0.940 |
| -36 | 1.448 | 12 | 0.884 |
| -24 | 1.280 | 24 | 0.781 |
| -12 | 1.131 | 36 | 0.690 |
| -6 | 1.064 | 48 | 0.610 |

* Calibration time

### 6.2 External Radiation

The specific gamma ray constant for Indium In 111 is 3.21 R/hr-mCi at 1 cm. The first half-value thickness of lead (Pb) for Indium In 111 is 0.023 cm. Selected coefficients of attenuation are listed in Table 6 as a function of lead shield thickness. For example, the use of 0.834 cm of Pb will attenuate the external radiation by a factor of about 1000.

**Table 6. Radiation Attenuation by Lead Shielding*.**

| Shield Thickness (Pb) cm | Coefficient of Attenuation |
|---|---|
| 0.023 | 0.5 |
| 0.203 | 0.1 |
| 0.513 | 0.01 |
| 0.834 | 0.001 |
| 1.12 | 0.0001 |

*From the Radiopharmaceutical Internal Dosimetry Information Center, Oak Ridge Associated Universities, Oak Ridge, TN 37831-0117, February 1985.

## 7 WARNINGS AND PRECAUTIONS

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

The contents of the two vials supplied with the kit are intended only for use in the preparation of Indium In 111 pentetreotide and are **NOT** to be administered separately to the patient.

**DO NOT ADMINISTER IN TOTAL PARENTERAL NUTRITION (TPN) ADMIXTURES OR INJECT INTO TPN INTRAVENOUS ADMINISTRATION LINES. IN THESE SOLUTIONS, A COMPLEX GLYCOSYL OCTREOTIDE CONJUGATE MAY FORM.**

The sensitivity of scintigraphy with Indium In 111 pentetreotide may be reduced in patients concurrently receiving therapeutic doses of octreotide acetate. Therefore, consideration should be given to temporarily suspending octreotide acetate therapy before the administration of Indium In 111 pentetreotide and to monitoring the patient for any signs of withdrawal.

### General

To help reduce the radiation dose to the thyroid, kidneys, bladder, and other target organs, patients should be well hydrated before the administration of Indium In 111 pentetreotide. They should increase fluid intake and void frequently for one day after the administration of this drug. In addition, it is recommended that patients be given a mild laxative (e.g., bisacodyl or lactulose) before and after administration of Indium In 111 pentetreotide (see Dosage and Administration section).

**Carcinogenesis and Mutagenesis**

Refer to the animal data in 16 NON-CLINICAL TOXICOLOGY of the product monograph.

**Contamination**

The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: toilet should be used instead of urinal; toilet should be flushed several times after use and if blood or urine gets onto clothing, such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen, and the patient's environment.

**Hepatic/Biliary/Pancreatic**

Octreotide acetate and the natural somatostatin hormone may be associated with cholelithiasis, presumably by altering fat absorption and possibly by decreasing motility of the gallbladder. A single dose of Indium In 111 pentetreotide is not expected to causecholelithiasis.

Therapy with octreotide acetate can produce severe hypoglycemia in patients with insulinomas. Since pentetreotide is an analog of octreotide, an intravenous line is recommended in any patient suspected of having an insulinoma. An intravenous solution containing glucose should be administered just before and during administration of Indium In 111 pentetreotide.

**Renal**

Since Indium In 111 pentetreotide is eliminated primarily by renal excretion, use in patients with impaired renal function should be carefully considered.

Indium In 111 pentetreotide elimination has not been studied in anephric patients or in those with poorly functioning kidneys. It is not known whether Indium In 111 pentetreotide can be removed by dialysis. Dosage adjustments in patients with decreased renal function have not been studied.

**Reproductive Health: Female and Male Potential**

- **Fertility**

Since adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this radiopharmaceutical preparation should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards.

### 7.1 Special Populations

#### 7.1.1 Pregnant Women

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of women of childbearing capability should be performed during the first ten days following the onset of menses, **or after ensuring the woman is not pregnant**. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

#### 7.1.2 Breastfeeding

Where an assessment of the risk to benefit ratio suggests the use of this product in lactating mothers, formula feeding should be substituted for breastfeeding.

#### 7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 7.1.4 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The most frequently occurring adverse reactions are: nausea, vomiting, headache, flushing and hyperhidrosis.

Pentetreotide is derived from octreotide which is used as a therapeutic agent to control symptoms from certain tumours. The usual dose for Indium In 111 pentetreotide is approximately 5 to 20 times less than for octreotide and is subtherapeutic.

### 8.2 Clinical Trial Adverse Reactions

Refer to section 8.3 below.

#### 8.2.1 Clinical Trial Adverse Reactions – Pediatrics

No data available.

### 8.3 Less Common Clinical Trial Adverse Reactions

The following adverse effects were observed in clinical trials at a frequency of less than 1% of 538 patients:

- Gastrointestinal disorders: Nausea;
- General disorders and administration site conditions: Pyrexia, Hyperhidrosis, Asthenia;
- Investigations: Alterations in liver enzymes;
- Musculoskeletal and connective tissue disorders: Arthralgia;
- Nervous system disorders: Dizziness, Headache; and
- Vascular disorders: Hypotension, Flushing.

These adverse effects were transient.

Also, in clinical trials, there was one reported case of bradycardia and one case of decreased hematocrit and hemoglobin.

### 8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

No data available.

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

**Clinical Trial Findings:** No data available.

**Post-Market Findings:** No data available.

### 8.5 Post-Market Adverse Reactions

In post-marketing experience the most frequently occurring adverse reactions are nausea, vomiting, headache, flushing and hyperhidrosis. In addition to the events listed above, the following have been identified during post-approval use of Octreoscan. Since these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Immune system disorders:* Hypersensitivity reactions: Pruritus; Rash; Urticaria; and Erythema. Rare cases of head and neck edema have been described in patients exposed to Octreoscan.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Interactions with other drugs have not been established.

### 9.3 Drug-Behavioural Interactions

No data available.

### 9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions affecting laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

The clinical utility of Indium In 111 pentetreotide is potentially significant. Scintigraphy with Indium In 111 pentetreotide can provide valuable patient information regarding the status of somatostatin receptors in tumours. This may be significant for patients when the embryonic origin of their tumour is unclear. Patients who have neuroendocrine tumours with somatostatin receptors can be started on octreotide therapy. Those patients with tumours deficient in somatostatin receptors can be spared the time and expense of octreotide therapy and proceed to alternate therapies.

### 10.1 Mechanism of Action

Pentetreotide is a DTPA conjugate of octreotide, which is a long-acting analog of the human hormone, somatostatin. Indium In 111 pentetreotide binds to somatostatin receptors on cell surfaces throughout the body.

### 10.2 Pharmacodynamics

Indium In 111 pentetreotide binds to cell surface receptors for somatostatin. In nonclinical pharmacologic studies, the hormonal effect of Octreoscan *in vitro* is one-tenth that of octreotide. Since a diagnostic imaging dose of Indium In 111 pentetreotide is subtherapeutic, Indium In 111 pentetreotide is not expected to exert clinically significant somatostatin effects.

### 10.3 Pharmacokinetics

Within an hour of injection, most of the dose of Indium In 111 pentetreotide distributes from plasma to extravascular body tissues and concentrates in tumours containing a high density of somatostatin receptors. Excretion is almost exclusively via the kidneys.

Indium In 111 pentetreotide radioactivity leaves the plasma rapidly. One-third of the radioactive injected dose remains in the blood pool at 10 minutes after administration. Plasma levels continue to decline so that by 20 hours post-injection, about 1% of the radioactive dose is found in the blood pool. The biological half-life of Indium In 111 pentetreotide is 6 hours.

**Absorption**

After background clearance, visualization of somatostatin receptor-rich tissue is achieved. In addition to somatostatin receptor-rich tumours, the normal pituitary, thyroid gland, liver, spleen and urinary bladder also are visualized in most patients, as is the bowel, to a lesser extent.

**Distribution**

No data available.

**Metabolism**

For several hours after administration, plasma radioactivity is predominantly in parent form. Ten percent of the radioactivity excreted is nonpeptide-bound.

**Elimination**

Half of the injected dose is recoverable in urine within six hours after injection, 85% is recovered in the first 24 hours, and over 90% is recovered in urine by two days. Hepatobiliary excretion represents a minor route of elimination, and less than 2% of the injected dose is recovered in feces within three days after injection.

**Special Populations and Conditions**

Special populations and conditions have not been studied.

## 11 STORAGE, STABILITY AND DISPOSAL

The Octreoscan Kit should be stored at **2°C to 8°C**. After reconstitution, store at controlled room temperature (20°C to 25°C).

Indium In 111 pentetreotide must be used within six hours of preparation.

Indium In 111 Chloride Sterile Solution, based on the stability test findings, is stable up to 10 days after the end of bombardment. Indium In 111 Chloride Sterile Solution should be stored upright in a lead shielded container at controlled room temperature.

An expiration date of two years has been established for the Octreoscan Reaction Vial, based on stability data. Protect from light. DO NOT use the kit beyond the expiration date stamped on the box.

Remaining product and components should be disposed of in a safe manner, in compliance with applicable regulations.

## 12 SPECIAL HANDLING INSTRUCTIONS

As with all intravenously administered products, Octreoscan should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Preparations containing particulate matter or discoloration should not be administered. They should be disposed of in a safe manner, in compliance with applicable regulations.

Aseptic techniques and effective shielding should be employed in withdrawing doses for administration to patients. Waterproof gloves should be worn during the administration procedure.

DO NOT administer Octreoscan in TPN (total parenteral nutrition) solutions or through the same intravenous line.

Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

DO NOT administer remaining product. Potential radioactive components or remaining product should be, whenever possible, safely stored for decay until they meet unconditional clearance levels per SOR/2000-207 as prescribed by Canada Nuclear Safety Commission. When unconditional clearance levels cannot be achieved, the radioactive waste should be disposed as approved by Canadian Nuclear Safety Commission and/or other applicable authority.

# PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

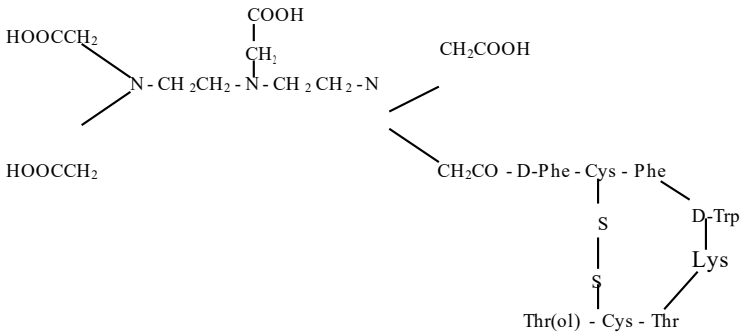
### Drug Substance 1

Proper name: Pentetreotide.

Chemical name: [N-(diethylenetriamine-N,N,N',N''-tetraacetic acid-N''-acetyl)-D-phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicystyl-L-threoninol cyclic (2→7) disulfide] (also known as octreotide DTPA).

Molecular formula and molecular mass: $C_{63}H_{87}N_{13}O_{19}S_2$

Structural formula:




Physicochemical properties:

Physical state: white or pate yellow fluffy lyophilizate.

Solubility: greater than 1% in water.

**Product Characteristics:**

The molecule contains 7 amino acids (including 1 threonine) and 1 amino alcohol (threoninol). It therefore has 10 chiral centers. The optical purity of the composite amino acids is controlled before production of the starting material octreotide to assure consistent enantiomeric forms in pentetreotide.

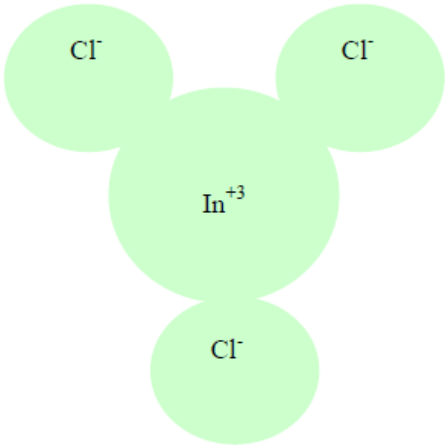
**Drug Substance 2**

Proper name: Indium In 111 chloride.

Chemical name: (111In) Indium Chloride / (111In) Indium Trichloride / Indium (111In) Chloride.

Molecular formula and molecular mass: $^{111}InCl_3$

Structural formula:




Physicochemical properties:

Physical state: liquid.

Chemical properties: Indium chloride is only stable to hydrolysis in acid solution. In neutral or basic solution it is subject to precipitation as indium hydroxide.

**Product Characteristics:**

Indium In 111 decays by electron capture to cadmium Cd 111 (stable) and has a physical half-life of 2.805 days (67.32 hours).

## 14 CLINICAL TRIALS

The following table 7 summarizes the overall sensitivity of Indium In 111 pentetreotide for the detection of various types of neuroendocrine tumours. These sensitivity rates were estimated by combining the detection rates reported from a number of experienced clinical investigators (Valkema, R., et al, "The diagnostic utility of somatostatin receptor scintigraphy in oncology" J Cancer Res Clin Oncol (1996) 122:523-532).

**TABLE 7- ACTIVITY OF INDIUM IN 111 PENTETREOTIDE FOR THE DETECTION OF VARIOUS TYPES OF NEUROENDOCRINE TUMOURS.**

| Neuroendocrine Tumours | *In vitro* receptor status (%) | Patients scanned with Indium In 111 pentetreotide | True Positive Patients | Estimated Sensitivity, combination of reports (%) |
|---|---|---|---|---|
| **Gastro-entero-pancreatic tumours** | | | | |
| Gastrinoma | 100 | 108 | 85 | 79 |
| Insulinoma | 67 | 53 | 25 | 47 |
| Glucagonoma | 100 | 8 | 8 | 100 |
| Unclassified | 100 | 140 | 117 | 84 |
| **Carcinoid** | 88 | 476 | 414 | 87 |

| | | | | |
|---|---|---|---|---|
| **Pheochromocytoma** | 73 | 37 | 32 | 86 |
| **Neuroblastoma** | 65 | 23 | 19 | 83 |
| **Medullary thyroid carcinoma** | 38 | 113 | 74 | 65 |
| **Paraganglioma** | 92 | 61 | 60 | 98 |
| **Pituitary tumours** | | | | |
| GH producing | 98 | 34 | 26 | 76 |
| TSH producing | | 6 | 6 | 100 |
| ACTH producing | | 11 | 1 | 9 |
| Non-functioning | 5 | 38 | 22 | 58 |
| **Small-cell lung carcinoma** | 56 | 127 | 122 | 96 |
| **Merkel cell tumour** | | 3 | 2 | 67 |

### 14.1 Trial Design and Study Demographics

Octreoscan (Kit for the preparation of Indium In 111 pentetreotide) was originally studied in nine unblinded clinical trials involving a total of 365 patients. Of these patients, 174 were male and 191 were female. Their mean age was 54.0 years (range 1.8 to 86 years). One patient was under the age of 2; 2 patients were between the ages of 2 and 12; 223 patients (61.1%) were between 18 and 60 years; and 136 patients (37.3%) were older than 60 years. A racial distribution is not available.

Eligible patients had a demonstrated or high clinical suspicion of a neuroendocrine tumour. The most common tumours were carcinoids (132 of 309 evaluable patients). Scintigraphic results were compared to results of conventional localization procedures (CT, ultrasound, MRI, angiography, surgery and/or biopsy). The mean dose of radioactivity administered was 173.4 MBq (4.7 mCi).

### 14.2 Study Results

Octreoscan results were consistent with the final diagnosis (success) in 267 of 309 evaluable patients (86.4%). Compared with carcinoids and gastrinomas, lower success rates were noted for localization of insulinomas, neuroblastomas, pituitary adenomas and medullary thyroid carcinomas. Octreoscan success was observed in 27 of 32 patients (84.4%) with clinically non-functioning neuroendocrine tumours (i.e. no symptom of a clinical syndrome mediated by abnormally elevated hormones). Importantly, Octreoscan localized previously unsuspected tumours in 57/204 patients. In 55/195 patients, Indium In 111 pentetreotide uptake occurred in lesions not thought to have somatostatin receptors. In a small subgroup of 39 patients who underwent tissue confirmation, the sensitivity rate for Octreoscan scintigraphy was 85.7%, while the comparable rate for CT/MRI was 68%. The specificity rate for Octreoscan scintigraphy was 50%; whereas the rate for CT/MRI was 12%. Larger studies are needed to confirm these comparisons. Overall, including all tumour types with or without the presence of somatostatin receptor, there were 3/508 false positives and 104/508 false negatives.

Of the 309 patients, 87 had received octreotide for therapeutic purposes within 72 hours of Octreoscan administration. These patients had an overall 95% success rate. The effect of different dose levels of octreotide on success rates has not been evaluated.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

The biodistribution of Octreoscan, at tracer dose levels, was evaluated in Wistar/Unilever rats over 72 hours. Rats, three male and three female per time point, received single intravenous injections of 0.5 mL Octreoscan and were sacrificed at 2, 24, 48 and 72 hours after injection. Radioactivity was assayed in blood, liver, heart, lungs, kidneys, spleen, adrenals, ovaries, testes, pancreas, eyes, thyroid, brain, pituitary, skeletal muscle (femoral), bone (left and right femur), tail, urinary bladder with content, mammary gland, uterus, stomach, duodenum, ascending colon, transverse colon, cecum, urine and feces.

Two hours following intravenous administration of Octreoscan, the highest amounts of activity were detected in the liver, duodenum and kidneys (1% of the injected dose). Approximately 63% of the injected radioactivity was excreted within 2 hours. Twenty-four hours after administration, 91% of the injected radioactivity was excreted, with the highest levels observed in the kidneys and caecum, with intermediate levels in the pancreas, liver, duodenum, and colon. At 48 and 72 post-injection, 95% of the radioactivity was excreted, with significant levels (approximately 2% of the injected dose) detected only in the kidneys. When considered as radioactivity per gram of tissue, Octreoscan was preferentially retained in the pituitary, pancreas, and to a lesser extent, in the adrenals. The urinary tract was the primary route of excretion.

**General Toxicology:**

**Acute toxicity studies: Mice:**

Two acute intravenous toxicity studies of pentetreotide in mice were conducted. Pentetreotide was tested in two forms: unformulated pentetreotide (i.e., without excipients) designated in the study report as SDZ 215-811; and pentetreotide reconstituted from the lyophilized kit. The lyophilized kit contained citric acid, sodium citrate, inositol and gentisic acid as well as pentetreotide.

In a study using unformulated pentetreotide, the drug was prepared by reconstituting the substance with 0.9 percent sodium chloride solution. Mice, two males and two females per treatment group, received single intravenous injections of pentetreotide via the lateral tail vein at doses between 100 and 560 mg/kg at an injection rate of approximately 2 mL/min. Mice were observed for seven days for mortality. These doses represent between 350,000 and 2,000,000 times the anticipated clinical dose.

The estimated $LD_{50}$ for pentetreotide was 427 mg/kg and the $LD_{100}$ was 560 mg/kg. No deaths were observed at 300 mg/kg. All deaths occurred within two minutes of administration of the drug. Clinical signs associated with death included: severe drowsiness, clonic convulsions, lateral position and forced breathing. Clinical signs observed following injections included: severe drowsiness; sedation; clonic convulsion; tonic convulsion; tremor; lateral position; lateral position and pawing the air, prone position; staggering; motor excitation; forced breathing; accelerated breathing; piloerection; scratching; cyanosis; thirst; and body weight loss. Clinical signs of intoxication were observed in the lowest dose group tested (100 mg/kg). Body weight losses were not dose-dependent and were not considered treatment related. No signs of intoxication were observed after two hours postadministration. Physical examinations were unremarkable. No treatment-related gross or microscopic abnormalities were noted at necropsy seven days after treatment.

The acute intravenous toxicity of formulated pentetreotide was evaluated in ICR mice. The pentetreotide was prepared by reconstituting the lyophilized kit with sterile water. Mice, five males and five females per treatment group, received single intravenous injections of saline or 0.30 mg/kg pentetreotide via the tail vein at a rate of 2 mL/min. The dose represents 1000 times the anticipated maximum clinical exposure.

No mortality was noted following intravenous injection of pentetreotide in mice at this dose. Following injection, both treated and control mice were observed to have piloerection and pallor of the extremities within five minutes of administration. This was accompanied by increased respiration for all mice treated with pentetreotide. Recovery was complete by day 2. Physical examinations of animals following dosing were unremarkable. No treatment-related effects on animal body weight or food consumption were observed. No treatment-related gross morphologic abnormalities were noted at necropsy 14 days after treatment.

**Acute toxicity studies: Rabbit:**

The acute intravenous safety of formulated pentetreotide was evaluated in New Zealand White Rabbits. Rabbits, four males and four females per treatment group, received single intravenous infusions of a saline solution (control) or 0.30 mg pentetreotide/kg via the marginal ear vein. The infusion rate was approximately 10 mL/min. This dose represents 1000 times the maximal anticipated clinical exposure. (In this study using the frozen liquid formulation, pentetreotide levels were at or slightly below the targeted range (27-33 µg/mL). However, for simplicity, the nominal value of 30 µg/mL is used in the calculation of dose levels in these summaries and in test article descriptions of the study report).

Two male and two female rabbits died within one hour following intravenous injection of pentetreotide. Following injection, both treated and control rabbits were observed to have piloerection within five minutes of administration. This was accompanied by tonic convulsions, increased respiration and noisy respiration for rabbits. Later signs of intoxication were, abnormal body carriage (hunched posture) for all surviving rabbits and lethargy in one surviving male and both surviving females. Recovery was complete within five hours of dosing. Physical examinations of animals following dosing were unremarkable. No treatment-related effects on animal, body weight or food consumption were observed. No treatment-related gross morphologic abnormalities were noted at necropsy 14 days after treatment.

**Subacute Toxicity Studies: Rats**

The subacute toxicity of intravenously administered formulated pentetreotide was evaluated in the rat and the rabbit. Results are summarized in tabular form at the end of this section (Table 8).

The subacute intravenous toxicity of formulated pentetreotide was evaluated in Sprague-Dawley rats. Rats, 10 males and 10 females per treatment group, received 14 consecutive daily infusions of formulated pentetreotide via the lateral tail vein at dose levels of 0 (saline), 25 or 50 µg/kg/day at a rate of 1 mL/min. (In this study using the frozen liquid formulation, pentetreotide levels were at or slightly below the targeted range (9-11 µg/mL). However, for simplicity, the nominal value of 10 µg/mL is used in the calculation of dose levels in these summaries and in test article descriptions of the study report). These dose levels represent 87.5 and 175 times the maximal anticipated clinical dose.

One death due to an anesthetic accident was observed in high-dose males. There were no clinical signs of toxicity noted during the post-dose observations or in the detailed clinical examinations. The body weight changes of the three groups were comparable. A slight statistically significant decrease in food

consumption was observed in low- and high-dose female groups, however the lack of effects on body weight gain suggest that the decrease was not treatment related.

A minor increase in platelet count was observed in high-dose females. A statistically significant increase in plasma lactate dehydrogenase activity was observed in high-dose males, but this was not accompanied by any macroscopic or microscopic changes, so it is not considered to be toxicologically significant. A small decrease in blood urea nitrogen levels was observed in high-dose females, but the majority of the values were within control values. There were no other significant treatment-related findings in the parameters evaluated: clinical signs; ophthalmoscopy; urinalysis; organ weights; and macroscopic and microscopic pathology.

Based on results of this study, it is concluded that 50 µg/kg/day intravenous pentetreotide (175 times the anticipated maximum clinical dose) represents a no effect level in the rat.

**Subacute Toxicity Studies: Rabbits**

The subacute intravenous toxicity of formulated pentetreotide was evaluated in rabbits. New Zealand White strain rabbits, five males and five females per treatment group, received 14 consecutive daily infusions of 50 or 100 µg/kg/day pentetreotide via the marginal ear vein at a rate of 20 mL/min. (In this study using the frozen liquid formulation, pentetreotide levels were at or slightly below the targeted range (9-11 µg/mL). However, for simplicity, the nominal value of 10 µg/mL is used in the calculation of dose levels in these summaries and in test article descriptions of the study report). These doses represent 175 and 350 times the maximum anticipated clinical dose. There were no mortalities during the two-week regimen. Prostate weight was decreased in high-dose males. A minor increase in brain weight observed in high-dose females was within historical control values. No treatment-related changes were observed in clinical signs, body weight gain, food consumption, ophthalmic abnormalities, hematology, biochemistry, urinalysis, and macroscopic and microscopic pathology.

Based on the results of this study, it is concluded that 100 µg/kg/day intravenous pentetreotide represents a no-effect level in rabbits (350 times the anticipated maximum clinical dose).

**Summary**: Assuming a 70 kg patient, the total dose under these conditions would be approximately 0.29 µg/kg, expressed as pentetreotide. The nonclinical studies on pentetreotide demonstrated an excellent degree of safety by the intravenous route under acute and subacute exposure conditions, in doses far exceeding the maximal anticipated clinical dose levels. The results are summarized in the following table:

**TABLE 8 - ACUTE AND SUBACUTE TOXICITY STUDIES**

| Type of Study | Species | Dose Regimen | Maximal Administered Dose, (µg/kg*) | Multiple of Maximal Clinical Dose |
|---|---|---|---|---|
| Acute toxicity (i.v.) | Mouse | Single | 300 | 1000 |
| | Rabbit | Single | 300 | 1000 |
| Subacute toxicity (i.v.) | Rat | 14 Daily | 50 | 175 |
| | Rabbit | 14 Daily | 100 | 350 |

*Expressed as µg pentetreotide/kg

**Carcinogenicity:** No data available.

**Genotoxicity:** The genotoxic potential of formulated pentetreotide was evaluated in the *in vitro* mouse lymphoma and the *in vivo* mouse micronucleus assays. Pentetreotide was inactive in both test systems. Literature reports on the potential toxicity of one excipient in Octreoscan, gentisic acid, were reviewed for possible clinical relevance. This analysis indicates that gentisic acid, at the concentration present in Octreoscan, is not likely to pose any significant clinical risk.

Mouse Lymphoma Assay: The mutagenic potential of pentetreotide was evaluated in an *in vitro* mammalian cell mutation assay. Pentetreotide was incubated with mouse lymphoma thymidine kinase L5178Y cells at concentrations of 10, 25, 50, or 100 µg/mL in presence or absence of exogenous metabolic activation (S-9 mix) for 3 hours. Cells were then incubated with trifluorothymidine (TFT). No statistically significant increase in mutant frequency (resistance to TFT) was observed after treatment with the pentetreotide in the presence or absence of metabolic activation. The positive controls (ethyl methane sulphonate in the absence of S-9 and 20-methylcholanthrene in the presence of S-9) significantly increased the mutation frequency. It is concluded that pentetreotide does not demonstrate mutagenic potential in this *in vitro* mutation assay.

Mouse Micronucleus: The clastogenic potential of pentetreotide was evaluated in an *in vivo* assay. Mice (five mice/sex/group) received intravenous injections of 50 mg pentetreotide/kg. Mitomycin C (4 mg/kg) was the positive control, saline was the negative control. Mice were sacrificed at 24, 48, or 72 hours and bone marrow smears were evaluated for the presence of micronuclei in polychromatic erythrocytes. The ratio of polychromatic to normochromatic erythrocytes was evaluated. Pentetreotide treatment did not increase the incidence of micronuclei or alter the ratio of polychromatic to normochromatic erythrocytes. The positive control significantly increased the incidence of micronuclei and decreased the ratio of polychromatic to normochromatic erythrocytes. It is concluded that pentetreotide did not induce chromosomal damage in this *in vivo* assay.

Review of Gentisic Acid Toxicity: A review of gentisic acid toxicity has been done to compare the possible toxicity of Octreoscan which contains gentisic acid. The Octreoscan preparation kit contains a maximum of 2.1 mg gentisic acid/10 µg pentetreotide. If a patient received 20 µg Octreoscan in an acute exposure, the amount of gentisic acid injected would be 4.2 mg. This yields an exposure of 0.06 mg/kg in a 70 kg patient. This maximum clinical exposure dose is 6,300 times lower than the intravenous $LD_{50}$ in mice, 5,000 times less than the intravenous no observed-effect level (NOEL), 50,000 times less than the intraperitoneal $LD_{50}$ in rats, and 75,000 times less than the oral $LD_{50}$ in mice. This dose is also 10,000 times lower than the lowest subcutaneous teratogenic dose in rats. It is concluded that acute intravenous

exposure to 0.06 mg/kg of gentisic acid as an excipient in Octreoscan is not likely to pose any significant clinical risk.

**TABLE 9 - SPECIAL TOXICITY STUDIES.**

| Study Number (NDA Reference) | Test Articles | Test System | Control Article | Pentetreotide Dose | Observations |
|---|---|---|---|---|---|
| BML 25/920870 | Pentetreotide Batch 91804 | Mouse Lymphoma Assay | Ethyl methane sulphonate; 20-Methyl cholanthrene | 1 µg/mL<br>5 µg/mL<br>10 µg/mL<br>25 µg/mL<br>50 µg/mL<br>100 µg/mL | No increase in mutation frequency in the presence and absence of metabolic activation; positive controls increase mutation rate. |
| BML 26/920806 | Pentetreotide Batch 91804 | Mouse Micro-nucleus Assay | Saline; Mitomycin C | 50 mg/kg | No increase in micronuclei in treated or negative control mice; Mitomycin C increased incidence of micronucle. |

**Reproductive and Developmental Toxicology:** No long-term animal studies have been performed to evaluate whether Indium In 111 pentetreotide affects fertility in males or females.

Pentetreotide was evaluated for mutagenic potential in an *in vitro* mouse lymphoma forward mutation assay and an *in vivo* mouse micronucleus assay. Evidence of mutagenicity was not found.

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

**Special Toxicology:** No data available.

**Juvenile Toxicity:** No data available.

## PATIENT MEDICATION INFORMATION

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**OCTREOSCAN™, Kit for the preparation of Indium In 111 pentetreotide**

Read this carefully before you receive **Octreoscan.** This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Octreoscan**.

| **Serious Warnings and Precautions** |
| --- |
| Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans. |

**What is Octreoscan used for?**

**Octreoscan** is used as an additional agent to localize neuroendocrine tumours (tumours that form from cells that release hormones into the blood in response to a signal from the nervous system) bearing somatostatin receptors (proteins on the surface of cells that bind to the hormone called somatostatin that help control other hormones in the body). Knowing the amount of somatostatin receptors in tissue(s) may help diagnose cancer and plan for treatment, if necessary.

**How does Octreoscan work?**

Indium In 111 pentetreotide binds to somatostatin receptors on cell surfaces throughout the body. Within an hour of injection, Octreoscan will attach to somatostatin receptors that are on the tumours. Your body will be scanned to produce an image of where the product accumulates that will help show where the tumours are in your body that have those somatostatin receptors.

**What are the ingredients in Octreoscan?**

Medicinal ingredients: Pentetreotide and Indium In 111 Chloride Sterile Solution.

Non-medicinal ingredients:

- Octreoscan Reaction Vial contains: Citric Acid Anhydrous; Gentisic Acid; Inositol; and Trisodium citrate anhydrous.
- Indium In 111 Chloride Sterile Solution contains ferric chloride.

**Octreoscan comes in the following dosage forms:**

The Reaction Vial is a powder for solution and the Indium In 111 Chloride Sterile Solution is a solution.

**Do not use Octreoscan if:**

No known contraindication.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive Octreoscan. Talk about any health conditions or problems you may have, including if you:**

- Are also taking therapeutic doses of octreotide acetate, which can lower the ability for Indium In 111 pentetreotide to help localize the tumours that have somatostatin receptors on them. Therefore, talk to your doctor about possibly temporarily suspending octreotide acetate therapy before receiving Octreoscan. Your doctor may need to monitor you for any signs of withdrawal from octreotide.
- Are suspected of having a small tumour in the pancreas that produces an excess amount of insulin (insulinoma).
- Are concerned about hard deposits (gallstones) that may form in the gallbladder (cholelithiasis).

As in the use of any other radioactive material, care will be taken to minimize radiation exposure to you consistent with proper patient management, and to minimize radiation exposure to occupational workers.

- In addition, the healthcare professional will take the following precautions: **DO NOT ADMINISTER IN TOTAL PARENTERAL NUTRITION (TPN) ADMIXTURES OR INJECT INTO TPN INTRAVENOUS ADMINISTRATION LINES; IN THESE SOLUTIONS, A COMPLEX GLYCOSYL OCTREOTIDE CONJUGATE MAY FORM.**
- **General:**
  To help reduce the radiation dose to your thyroid, kidneys, bladder and other target organs, you should drink liquids before receiving Octreoscan. You should increase drinking fluids and urinate frequently for one day after receiving this drug. In addition, it is recommended that you be given a mild medication that either loosens stool or stimulates a bowel movement (laxative) (e.g., bisacodyl or lactulose) before and after receiving Octreoscan.
- **Contamination:**
  You should be taking the following measures for up to 12 hours after receiving Octreoscan:
  - Toilet should be used instead of urinal;
  - Toilet should be flushed several times after use; and
  - If blood or urine gets onto clothing such clothing should be washed separately or stored for 1 to 2 weeks to allow for decay.
- **Hepatic/Biliary/Pancreatic:**

  Octreotide acetate and the natural somatostatin hormone may be associated with gallstones by altering fat absorption and by limiting the ability of the gallbladder to squeeze out its contents. A single dose of Octreoscan contains a very small amount of pentetreotide (similar to octreotide) and is not expected to cause gallstones. Therapy with octreotide acetate can produce severe low blood sugar (hypoglycemia) in patients with insulinomas. Since pentetreotide can act in a similar way to octreotide, you may receive an intravenous solution containing sugar (glucose) just before and during administration of Octreoscan.

- **Renal:**

  Since your body eliminates Octreoscan through your kidneys, tell your physician if you have any kidney problems or kidney disease.

- **Reproductive Health: Female and Male Potential:**

  Octreoscan preparation should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential risks.

- **Pregnant Women:**

  If you are of childbearing capability, examination with Octreoscan should be performed during the first ten days following the onset of menses, *or after it has been determined that you are not pregnant.* The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

- **Breastfeeding:**

  If you are breastfeeding; you may be advised to substitute with formula feeding.

- **Pediatrics:**

  The safety and effectiveness for pediatric patients has not been established.

- **Geriatrics:**

  The safety and effectiveness for geriatic patients has not been established.

**Other warnings you should know about:**

No other warnings have been established.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with Octreoscan:**

Interactions with other drugs have not been established.

**How to take Octreoscan:**

Octreoscan will be given to you by a healthcare professional who is experienced in the use of radiopharmaceuticals.
Make sure you are well hydrated before your exam.

**Usual dose:**

Depending on the type of exam you will receive, one of the below dosages will be given to you:

- Planar imaging: 111 MBq (3.0 mCi) of Indium In 111 pentetreotide prepared from an Octreoscan kit.
- SPECT imaging: 222 MBq (6.0 mCi) of Indium In 111 pentetreotide prepared from an Octreoscan kit.

**Overdose:**

If you think you, or a person you are caring for, have received too much **Octreoscan**, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

Since you will receive a single dose specially calculated for you and your examination, there is no missed dosing.

**What are possible side effects from using Octreoscan?**

These are not all the possible side effects you may have when taking Octreoscan. If you experience any side effects not listed here, tell your healthcare professional.

- Nausea;
- Vomiting;
- Headache;
- Temporary reddening of the skin; and/or
- Excessive sweating that's not necessarily related to heat or exercise.

The following side effects may also occur:

- Raised body temperature (Fever);
- Abnormal physical weakness or lack of energy;
- Alterations in liver enzymes;
- Joint pain;
- Dizziness;
- Low blood pressure; and/or
- Allergic reactions such as itching, rash, hives and superficial reddening of the skin.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

The Octreoscan Kit should be stored between **2°C and 8°C**. After reconstitution for the injection, it should be stored at room temperature (20°C to 25°C).

**If you want more information about Octreoscan:**

- Talk to your healthcare professional; and/or
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-866-885-5988.

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