Octreoscan™
Kit for the Preparation of Indium In 111 Pentetreotide
Diagnostic - For Intravenous Use.
Rx only

DESCRIPTION
Octreoscan™ is a kit for the preparation of indium In-111 pentetreotide, a diagnostic radiopharmaceutical. It consists of two components:

1) A 10-mL Octreoscan Reaction Vial which contains a lyophilized mixture of:
   (i) 10 μg pentetreotide (N-diethylenetriamine-N,N,N',N'-
    tetraacetic acid-N'-acetyl-D-phenylalanyl-L-hemicyctyl-L-
    phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicyctyl-L-
    threoninol cyclic (2+7) disulfide), (also known as octreotide OTRA),
   (ii) 2.0 mg gentamic acid (2, 5-dihydroxybenzoic acid),
   (iii) 4.9 mg thiosulfate citrate, anhydrous,
   (iv) 0.37 mg citric acid, anhydrous, and
   (v) 10.0 mg inositol.

Pentetreotide has the following structural formula:

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

2) A 10-mL vial of Indium In 111 Chloride Sterile Solution, which contains: 1.1 mL or 111 MBq/mL (3.0 mCi/mL) indium In-111 chloride in 0.20N HCl at time of calibration. The vial also contains ferric chloride at a concentration of 3.5 μg/mL (ferric ion, 1.2 μg/mL). The vial contents are sterile and nonpyrogenic. No bacteriostatic preservative is present.

Indium In-111 pentetreotide is prepared by combining the two kit components. INSTRUCTIONS FOR THE PREPARATION OF INDUIM IN-111 PENTETRETOIDE. Indium In-111 reacts with the diethylenetriaminepentaacetic 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, U.S.P., immediately before intravenous administration. In either case, the labeling yield of indium In-111 pentetreotide should be determined before administration to the patient. A method recommended for determining the labeling yield is presented at the end of this package insert.

Physical Characteristics
Indium In-111 decays by electron capture to cadmium-111 (stable) and has a physical half-life of 2.805 days (67.32 hours) (see Table 2).1 The principal photons that are useful for detection and imaging are listed in Table 1.

Table 1. Principal Radiation Emission Data

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Mean Percent Per Disintegration</th>
<th>Energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma-2</td>
<td>90.2</td>
<td>171.3</td>
</tr>
<tr>
<td>Gamma-3</td>
<td>94.0</td>
<td>245.4</td>
</tr>
</tbody>
</table>


Table 2. Radiation Attenuation by Lead Shielding

<table>
<thead>
<tr>
<th>Shield Thickness (Ps) cm</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.023</td>
<td>0.5</td>
</tr>
<tr>
<td>0.200</td>
<td>0.1</td>
</tr>
<tr>
<td>0.513</td>
<td>0.01</td>
</tr>
<tr>
<td>0.634</td>
<td>0.0001</td>
</tr>
<tr>
<td>1.12</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 3 lists fractions remaining at selected time intervals before and after calibration. This information may be used to correct for physical decay of the radionuclide.

Table 3. Physical Decay Chart: Indium In-111, Half-life 2.805 Days (67.32 hours).

<table>
<thead>
<tr>
<th>Hours Remaining</th>
<th>Hours Fraction Remaining</th>
<th>Hours Fraction Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>72</td>
<td>0.600</td>
<td>0.600</td>
</tr>
<tr>
<td>144</td>
<td>0.200</td>
<td>0.200</td>
</tr>
<tr>
<td>216</td>
<td>0.060</td>
<td>0.060</td>
</tr>
<tr>
<td>288</td>
<td>0.010</td>
<td>0.010</td>
</tr>
</tbody>
</table>

* Calibrations time

PHARMACODYNAMICS

Pharmacokinetics
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 24 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.

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.

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

Pharmacodynamics
Indium In-111 pentetreotide binds to cell surface receptors for somatostatin. Indium In-111 pentetreotide binds to somatostatin receptors on cell surfaces throughout the body. Within an hour of injection, most of the dose of indium In-111 pentetreotide distributes from plasma to extravascular body tissues and concentrates in tumors containing a high density of somatostatin receptors. After background clearance, visualization of somatostatin receptor-rich tissue is achieved. In addition to somatostatin receptor-rich tumors, the normal pituitary gland, thyroid gland, liver, spleen and urinary bladder also are visualized in most patients, as is the bowel, to a lesser extent. Excretion is almost exclusively via the kidneys.

INDICATIONS AND USAGE

Indium In-111 pentetreotide is an agent for the scintigraphic localization of primary and metastatic neuroendocrine tumors bearing somatostatin receptors.

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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 diagnostic imaging doses of indium In-111 pentetreotide are lower than the therapeutic doses of octreotide, indium In-111 pentetreotide is not expected to exert clinically significant somatostatin and gastrin effects. Novices are not expected to cause cholelithiasis.

INDICATIONS AND USAGE

Indium In-111 pentetreotide is a dopamine-D2 antagonist (receptor), 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.

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.

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

4. To 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 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).

5. Indium In-111 pentetreotide should be tested for labeling yield of radioactivity prior to administration. The product must be used within six hours of preparation.

6. Components of the kit are sterile and nonpyrogenic. To maintain sterility, it is essential that directions are followed carefully. Aseptic technique must be used during the preparation and administration of indium In-111 pentetreotide.

7. 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 cause cholelithiasis.

8. As with any other radioactive material, appropriate shielding should be used to avoid unnecessary radiation exposure to the patient, occupational workers, and other persons.

9. Radiochemicals should be used only by physicians who are qualified by specific training in the safe use and handling of radiopharmaceuticals.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been performed with indium In-111 pentetreotide to evaluate carcinogenic potential or effects on fertility. Pentetreotide was evaluated for mutagenic potential in in vitro mouse lymphoma forward mutation assay and an in vivo mouse micronucleus assay; evidence of mutagenicity was not found.
Pregnancy Category C
Animal reproduction studies have not been conducted with indium In-111 pentetreotide. It is not known whether indium In-111 pentetreotide can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore, indium In-111 pentetreotide should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when indium In-111 pentetreotide is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
The following adverse effects were observed in clinical trials at a frequency of less than 1% of 358 patients: dizziness, fever, flushing, headache, hypertension, changes in liver enzymes, joint pain, nausea, sweating, and weakness. These adverse effects were transient. Also in clinical trials, there was one reported case of bloodcardiac and one case of decreased hematocrit and hemoglobin.

Pentetreotide is derived from octreotide which is used as a therapeutic agent to control symptoms from certain tumors. The usual dose for indium In-111 pentetreotide is approximately 5 to 20 times less than for octreotide and is subtherapeutic. The following adverse reactions have been associated with octreotide in 3% to 10% of patients: nausea, injection site pain, diarrhea, abdominal pain, discomfort, loose stools, and vomiting. Hypertension and hyper- and hypoglycemia have also been reported with the use of octreotide.

DOSAGE AND ADMINISTRATION
Before administration, a 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 intake is necessary during this period as a support both to renal elimination and the bowel-clearing process. In a patient with an insulinoma, bowel-clearing should be undertaken only after consultation with an endocrinologist.

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.

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

As with all intravenously administered products, Octreoscan should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If any of these components 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 solutions or through the same intravenous line.

Radiation Dosimetry
The estimated radiation doses to the average adult (70 kg) from intravenous administration of 111 MBq (3 mCi) and 222 MBq (6 mCi) are presented in Table 4. These estimates were calculated by Oak Ridge Associated Universities using the data published by Krenning, et al.

HOW SUPPLIED
The Octreoscan kit (NDC 69945-050-40) is supplied with the following components:
1. A 10-ml Octreoscan Reaction Vial which contains a lyophilized mixture of (i) 10 μg pentetreotide [N-dithiobenzenamidin-N,N,N',N"-tetraacetic acid-N'-acetyl-D-phenylalanly-L-hemicystyl-L-phenylalany-D-tryptophyl-L-lyssyl-L-threonyl-L-hemicystyl-L-threoninol cyclic (2+7) disulfide], also known as octreotide (DTPA), (ii) 2.2 mg gentamicin (C.2, 5-dihydroxybenzoic acid), (iii) 4.9 mg trisodium citrate, anhydrous, (iv) 0.37 mg citric acid, anhydrous, and (v) 10.0 mg inositol.

Before lyophilization, sodium hydroxide or hydrochloric acid may have been added for pH adjustment. The vial contents are sterile and nonpyrogenic. No bacteriostatic preservative is present. No antimicrobial preservative is present. 2. A 0.5 ml syringe of Indium In-111 Chloride Sterile Solution with an ionization chamber immediately before administration.

2. Aseptically remove the contents of the Indium In 111 Chloride Sterile Solution from the ionization chamber immediately before administration.

3. Place the Octreoscan Reaction Vial in a lead dispensing shield approved manner, or allowed to decay to safe levels of radioactivity.

4. Transfer Indium In 111 Chloride Sterile Solution with an using the transfer needle in 1. Waters Sep-Pak™ C18 Cartridge, Part No. 51910
2. Methanol, 15 mL (Caution: toxic and flammable. Exercise due caution.)
3. Percent non-elutable impurities = 
4. Disposable syringes:
5. Ion chamber
6. Ion chamber 

7. Using proper shielding, visually inspect the vial contents. The solution should be clear, colorless, and free of particulate matter. If not, the solution should not be used. It should be disposed of in a safe and approved manner.

8. 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.

9. The labeling yield of the reconstituted solution should be checked before administration to the patient, according to the instructions given below. If the radiochemical purity is less than 90%, the product should not be used.

10. Store the radioactivity vial containing the indium In-111 pentetreotide solution at or below 25°C (77°F) until use. The indium In-111 pentetreotide must be used within six hours of preparation.

11. If desired, the preparation can be diluted to a maximum volume of 3 mL with 0.9% Sodium Chloride Injection, U.S.P. immediately prior to injection. The sample should be drawn up into a shielded, sterile syringe and administered to the patient.

RECOMMENDED METHOD FOR DETERMINATION OF LABELING YIELD OF INDIUM IN 111 PENTETRETOIDE

Required Materials
1. Waters Sep-Pak™ C18 Cartridge, Part No. 51910
2. Methanol, 15 mL (Caution: toxic and flammable. Exercise due caution.)
3. Distilled water, 20 mL
4. Disposable syringes:
5. Three disposable culture tubes or vials, minimum 10 mL capacity
6. Ion chamber

Preparation of the Sep-Pak Cartridge
1. Place the Sep-Pak cartridge with 10 mL methanol as follows: a) Fill 10 mL syringe with 10 mL 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. 2. Similarly, rinse the cartridge with 10 mL 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 additional 5 mL of water. Discard the eluate.