ChiRhoStim® (Human Secretin) for injection, for intravenous use.

Initial U.S. Approval: 2004

Indications and Usage

ChiRhoStim® is a secretin class hormone indicated for stimulation of:
- pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreas exocrine dysfunction (1)
- gastrin secretion to aid in the diagnosis of gastrinoma (1)
- pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP) (1)

Dosage and Administration

To avoid an incorrect stimulation test result, discontinue the following drugs for the recommended amount of time prior to administration of ChiRhoStim®:
- anticholinergic drugs: at least 5 half-lives. (2.1, 5.1, 7.1)
- H2-receptor antagonists: at least 2 days. (2.1, 5.2, 7.2)
- proton pump inhibitors (PPIs): consult the prescribing information for specific PPIs. (2.1, 5.2, 7.2)

The recommended dosage by indication is shown in the table:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dosage Regimen (2.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of exocrine pancreatic dysfunction</td>
<td>0.2 mcg/kg by intravenous injection over 1 minute</td>
</tr>
<tr>
<td>Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma</td>
<td>0.4 mcg/kg by intravenous injection over 1 minute</td>
</tr>
<tr>
<td>Stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP)</td>
<td>0.2 mcg/kg by intravenous injection over 1 minute</td>
</tr>
</tbody>
</table>

Adverse Reactions

Most common adverse reactions (≥2 patients) are nausea, vomiting, flushing, and upset stomach. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact:
ChiRhoClin, Inc. at 1-877-272-4888 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2017

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**FULL PRESCRIBING INFORMATION**

1 INDICATIONS AND USAGE

**ChiRhoStim®** is indicated for the stimulation of:

- pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction.
- gastrin secretion to aid in the diagnosis of gastrinoma, and
- pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation Prior to Secretin Stimulation Testing

Discontinue Interacting Drugs

To avoid an incorrect stimulation test result, discontinue the following drugs prior to administration of **ChiRhoStim®**:

- anticholinergic drugs: at least 5 half-lives prior to testing
- H2-receptor antagonists: at least 2 days prior to testing
- proton pump inhibitors (PPIs): Consult the prescribing information for specific PPIs before administering **ChiRhoStim®**.[see Warnings and Precautions (5.2), Drug Interactions (7.2)].

2.2 Preparation and Dosage Regimen

The recommended dosage regimen of **ChiRhoStim®** by indication is shown below in Table 1.

**TABLE 1: Dosage by Indication**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Secretions</td>
<td>0.2 mcg/kg by intravenous injection over 1 minute</td>
</tr>
<tr>
<td>Gastrin Secretion</td>
<td>0.4 mcg/kg by intravenous injection over 1 minute</td>
</tr>
</tbody>
</table>

Preparation of Recommended Dosage:

- **ChiRhoStim®** is a lyophilized powder, which requires reconstitution prior to intravenous administration.
- Determine the number of vials needed for the prescribed dosage based on the patient's weight and recommended dosage. Follow these steps to determine the patient dose:
  - Total dose (mcg) = patient's weight (kg) x prescribed dose (mcg/kg).
  - Total injection volume (mL) = total dose (mcg) divided by the concentration of the reconstituted solution (2 mcg/mL).
  - Round the total injection volume to the nearest tenth of a mL.
  - Total number of vials = total injection volume divided by the vial volume (8 mL).
- To reconstitute one 16 mcg vial:
  - Dissolve the contents of the **ChiRhoStim®** 16 mcg vial in 8 mL of 0.9% Sodium Chloride Injection, USP, to yield a concentration of 2 mcg/mL.
  - Shake vigorously to ensure dissolution.
  - Inspect the reconstituted solution visually for particulate matter or discoloration prior to administration. If particulate matter or discoloration is seen, discard the reconstituted solution.
- To reconstitute one 40 mcg vial:
  - Dissolve the contents of the **ChiRhoStim®** 40 mcg vial in 10 mL of 0.9% Sodium Chloride Injection, USP, to yield a concentration of 4 mcg/mL.
  - Shake vigorously to ensure dissolution.
  - Inspect the reconstituted solution visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is seen, discard the reconstituted solution.
- Repeat steps above to reconstitute additional vials, as needed, to administer the total dose.
- Use immediately after reconstitution and discard any unused portion.

2.3 Administration and Test Methods

Stimulation testing with **ChiRhoStim®** should only be performed by physicians with sufficient expertise. Ensure that the institution has established normative ranges for pancreatic exocrine response.

**Stimulation of Pancreatic Secretions, including Bicarbonate, to Aid in the Diagnosis of Exocrine Pancreatic Dysfunction:**

**Preparation:**

- Instruct patients to fast for at least 12 to 15 hours prior to beginning the test.

**Sample Collection:** [performed using either the gastrointestinal Drelling tube (fluoroscopic) or endoscopic collection method]

- **Gastroduodenal (Drelling) Tube Collection Method**
  - Pass a radiopaque, double-lumen gastrointestinal tube through the mouth using a guidewire.
  - Under fluoroscopic guidance, place the opening of the proximal lumen in the gastric antrum and the opening of the distal lumen beyond the ampulla of Vater. Confirm the tube positioning and secure the tube.
  - Connect both the proximal (gastric) and distal (duodenal) lumens to low intermittent suction, and apply negative pressure of 25 to 40 mmHg to both lumens.
  - Collect a sample of the duodenal contents and check the pH of the aspirate to verify tube placement. Proceed to next step if the duodenal aspirate has a pH of 6 or higher. If the pH is less than 6, repopulate the tube.
  - Collect a baseline sample of duodenal fluid for a 15-minute period.
  - **Administer ChiRhoStim®** at a dose of 0.2 mcg/kg body weight intravenously over 1 minute [see Dosage and Administration (2.2)]. For the 60-minute period following the injection, collect four consecutive 15-minute samples of duodenal fluid. Clear the duodenal lumen of the tube with an injection of air after each 15-minute sample collection. Note that wide variation in aspirate volumes is indicative of incomplete aspiration between samples.

- **Endoscopic Collection Method:**
  - Endoscopic Pancreatic Function Test (ePFT) [1]
    - Administer a topical anesthetic spray to the posterior pharynx and place a bite block in the mouth.
    - Perform a standard upper endoscopy by passing the endoscope into the stomach with the patient in the left lateral decubitus position.
    - After gastric insufflation, aspirate all gastric fluid through the endoscope and discard.
    - Pass the endoscope through the pylorus into small intestine and position the tip of the endoscope at the junction of the second and third portion of the duodenum.
    - Aspirate duodenal fluid for several seconds to clear the residual gastric fluid from the tube.
    - Collect a baseline aspirate of duodenal fluid (2 to 5 mL) from the post-bulbar duodenum.
    - **Administer ChiRhoStim®** at a dose of 0.2 mcg/kg body weight intravenously over 1 minute [see Dosage and Administration (2.2)].
    - Starting 15 minutes after administration of **ChiRhoStim®**, collect 4 timed duodenal fluid aspirates (each 3 to 5 mL) at 15-minute intervals. Keep the patient in the left lateral decubitus position throughout the procedure.

**Sample Handling and Interpretation:**

- Place fluid specimens on ice for immediate measurement of bicarbonate concentration. Samples will not be analyzed immediately, store fluid at 4°C.
- Peak bicarbonate concentrations of 80 to 130 mEq/L after stimulation indicate normal pancreatic exocrine function.
- Peak bicarbonate concentrations greater than 130 mEq/L after stimulation indicate pancreatic exocrine dysfunction.

**Stimulation of Gastrin Secretion to Aid in the Diagnosis of Gastrinoma:**

**Preparation:**

- Instruct patients to fast for at least 12 hours prior to beginning the test.

**Sample Collection:**

- Before administering **ChiRhoStim®**, draw two blood samples for determination of fasting serum gastrin levels (baseline values).
- **Administer ChiRhoStim®** at a dose of 0.4 mcg/kg body weight intravenously over 1 minute [see Dosage and Administration (2.2)].
- Collect post-injection blood samples after 1, 2, 5, 10, and 30 minutes for determination of serum gastrin concentrations.

**Sample Interpretation:**

- Gastrinoma is strongly suspected in patients who show an increase in serum gastrin concentration of more than 110 pg/mL over baseline levels or on any of the post-injection samples.

3 DOSAGE FORMS AND STRENGTHS

For injection: 16 mg or 40 mg of human secretin as a white lyophilized powder in single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity to Secretin Stimulation Testing

Patients who have undergone vagotomy, have inflammatory bowel disease or are receiving anticholinergic drugs at the time of **ChiRhoStim®** stimulation testing, may be hypersensitive to **ChiRhoStim®** stimulation, falsely suggesting pancreatic disease. Discontinue anticholinergic drugs at least 5 half-lives prior to stimulation testing [see Dosage and Administration (2.1)]. Consider additional testing and clinical assessments for aid in diagnosis.

5.2 Hypersensitivity to Secretin Stimulation Testing

Gastrin Stimulation

Patients receiving H2-receptor antagonists or PPIs at the time of stimulation testing with **ChiRhoStim®** to aid in the diagnosis of gastrinoma may be hypersensitive to secretin stimulation, falsely suggesting gastrinoma. Discontinue H2-receptor antagonists at least 2 days prior to stimulation testing. Consult the prescribing information of each specific PPI before administering **ChiRhoStim®** [see Dosage and Administration (2.1)].

Pancreatic Secretions

Patients with alcoholic or other liver disease may be hypersensitive to stimulation with **ChiRhoStim®**, masking the presence of coexisting pancreatic disease. Consider additional testing and clinical assessments for aid in diagnosis.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed during the clinical trials of a drug cannot always be directly compared to the rates observed during the clinical trials of another drug and may not reflect the adverse reaction rates observed in practice.

The data described below reflect exposure to **ChiRhoStim®** in 531 patients from an open-label clinical trial. The population consisted of patients aged 1 to 91 years, 185 males, 346 females, 480 Caucasians, 31 Blacks, 12 American Indians, 6 Hispanics, and 2 Asians with known or suspected diseases of the exocrine pancreas including chronic pancreatitis and pancreatic cancer. Most patients received a single dose of **ChiRhoStim®** in a dose range of 0.2 mcg/kg to 0.4 mcg/kg. The most common adverse reactions (reported in all at least 2 patients in the trial) are listed in Table 2.

**TABLE 2**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ChiRhoStim® Number of Patients N = 531</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Flushing</td>
<td>2</td>
</tr>
<tr>
<td>Upset Stomach</td>
<td>2</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

7.1 Hypersensitivity to Anticholinergics

The concomitant use of anticholinergic drugs may cause a hypersensitivity to stimulation testing with **ChiRhoStim®**. Discontinue anticholinergic drugs at least 5 half-lives prior to administering **ChiRhoStim®** [see Dosage and Administration (2.1)].

7.2 Hypersensitivity of Gastrin Stimulation with H2-Receptor Antagonists and PPIs

The concomitant use of H2-receptor antagonists or PPIs may cause a hypersensitivity in gastrin stimulation in response to stimulation testing with **ChiRhoStim®**, falsely suggesting gastrinoma. Discontinue H2-receptor antagonists at least 2 days before administering **ChiRhoStim®** to aid in the diagnosis of gastrinoma.

The time it takes for serum gastrin concentrations to return to baseline following discontinuation of PPIs is specific to the individual drug. Consult the prescribing information of each specific PPI before administering **ChiRhoStim®** to aid in the diagnosis of gastrinoma.
12.3 Pharmacokinetics
The pharmacokinetic profile for synthetic human secretin was evaluated in 12 healthy subjects following a single-dose of human secretin administered as a 0.4 mcg/kg intravenous bolus. The plasma concentrations of human secretin declined to baseline concentrations within 90 to 120 minutes. The elimination half-life of synthetic human secretin is 45 minutes. The clearance of synthetic human secretin is 593 ± 51 mL/min and the volume of distribution is 2.7 liters.

14 CLINICAL STUDIES
14.1 Stimulation of Pancreatic Secretions, Including Bicarbonate to Aid in the Diagnosis of Exocrine Pancreatic Dysfunction
ChiRhoStim® administered intravenously stimulates the exocrine pancreas to secrete pancreatic juice, which can aid in the diagnosis of exocrine pancreatic dysfunction. Normal ranges for pancreatic secretory response to intravenous secretin in patients with defined pancreatic disease have been shown to vary. One source of variation is related to the inter-investigator differences in operative technique.

In two studies, a total of 18 patients with a documented history of chronic pancreatitis were given 0.2 mcg/kg synthetic human secretin (sHS), 0.2 mcg/kg synthetic porcine secretin (sPS), and 1CU/kg (equal to 0.2 mcg/kg for biologically derived secretin (bPS)) in a crossover design. The results appear in Figures 1 and 2. In another study, 35 healthy subjects were given sHS at a dose of 0.2 mcg/kg. The results appear in Figures 1 and 2.

14.2 Stimulation of Gastrin Secretion to Aid in the Diagnosis of Gastrinoma
ChiRhoStim® administered intravenously stimulates gastrin release in patients with gastrinoma (Zollinger-Ellison Syndrome), whereas no or only small changes in serum gastrin concentrations occur in healthy subjects and in patients with duodenal ulcer disease. Discriminant analysis was used to establish secretin stimulation testing as an aid in the diagnosis of gastrinoma. An increase from basal levels of greater than or equal to 110 pg/mL was the optimal point separating positive and negative tests. This gastrin response is the basis for the use of secretin as a provocative test in the evaluation of patients in whom gastrinoma is a diagnostic consideration.

In a three way crossover study, 6 patients with tissue confirmed gastrinoma received synthetic human secretin (ChiRhoStim®), synthetic porcine secretin and biologically derived porcine secretin at a dose of 0.4 mcg/kg for each drug. Serum gastrin levels were reported to be greater than 110 pg/mL for all secretin products tested after stimulation. Testing of ChiRhoStim® in 12 healthy subjects demonstrated completely negative results for gastrinoma.

14.3 Stimulation of Pancreatic Secretion to Facilitate Identification of the Ampulla of Vater and Accessory Papilla During Endoscopic Retrograde Cholangiopancreatography (ERCP)
In a randomized, placebo controlled crossover study in 24 patients with pancreas divisum undergoing ERCP, ChiRhoStim® at a dose of 0.2 mcg/kg resulted in 18 of 24 successful cannulations of the minor duct compared to 2 of 24 for placebo.

15 REFERENCES

16 HOW SUPPLIED/STORAGE and HANDLING
ChiRhoStim® (human secretin), for injection is supplied as a white lyophilized sterile powder in a single-dose vial for reconstitution.

Storage: Store at -20°C (freezer). Protect from light.

17 PATIENT COUNSELING INFORMATION
Advise the patient to tell their healthcare provider all the medications they are taking, including anticholinergic drugs, H2-receptor antagonists or PPIs [see Warnings and Precautions (5.1, 5.2)].

Manufactured for:
ChiRhoClin, Inc.
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005PS007