ChiRhoStim® (Human Secretin) Injection, lyophilized powder for intravenous use, 16 mcg and 40 mcg vials

Initial U.S. Approval: 2004

Dosage and Administration (2.0) 06/2007

ChiRhoStim® injections are indicated for:

- Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of exocrine pancreas dysfunction (1.1)
- Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma (1.2)
- Facilitation of identification of the ampulla of Vater and the accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP) (1.3)

DOSAGE FORMS AND STRENGTHS

ChiRhoStim® is available in two strengths:

- As a lyophilized sterile powder in 10 mL vials containing 16 mcg of human secretin. Reconstitute with 8 mL of saline for injection to yield a final concentration of 2 mcg of human secretin/mL (3.1)
- As a lyophilized sterile powder in 10 mL vials containing 40 mcg of human secretin. Reconstitute with 10 mL of saline for injection to yield final concentration of 4 mcg of human secretin/mL (3.2)

CONTRAINDICATIONS

Patients suffering from acute pancreatitis should not receive ChiRhoStim® until the acute episode has subsided (4).

WARNINGS AND PRECAUTIONS

- Allergic Reactions (5.1)
- Vagotomy or Inflammatory Bowel Disease (5.2)
- Alcoholic or Other Liver Disease (5.3)

ADVERSE REACTIONS

Most common adverse reactions (>0.5%) are nausea, flushing, abdominal pain, and vomiting (6).

To report SUSPECTED ADVERSE REACTIONS, contact ChiRhoClin, Inc. at 301-478-8388 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

The concomitant use of anticholinergic agents may make patients hyporesponsive, i.e., may produce a false result (7). Results of secretin testing in these patients should be interpreted with caution.

USE IN SPECIFIC POPULATIONS

The safety evaluation of ChiRhoStim® in geriatric patients showed no difference from the safety evaluation in the general population (8.5).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 6/2007
A radiopaque, double lumen tube is passed through the mouth following a 10-15 hour fast. Under fluoroscopy control, the opening of the proximal lumen of the tube is placed in the gastric antrum and the opening of the distal lumen just beyond the papilla of Vater. Under fluoroscopic control, the opening of the proximal lumen of the tube is placed in the gastric antrum and the opening of the distal lumen just beyond the papilla of Vater. The endoscopist in identifying the ampulla of Vater for various reasons including: anatomic variations, it is often necessary to perform secretin testing to aid in the diagnosis of various conditions. In addition to the diagnosis of determining the peak bicarbonate concentration for any sample collected.

1.2 Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma.

1.3 Alcohol or Liver Disease

A greater than normal volume response to secretin stimulation, which may mask concomitant pancreatic disease, is strongly associated with alcoholic liver disease. Results of secretin stimulation tests in these patients should thus be interpreted with caution.

1.4 ADVERSE REACTIONS

Mild to moderate adverse reactions have been noted for synthetic human secretin in clinical studies in 533 patients and 61 healthy volunteers. Two severe adverse reactions, nausea and abnormal thirst, were observed in one patient. Table 1 details the types and number of patients with adverse reactions.

| Table 1: Adverse Reactions with ChiRhoStim® |
|-----------------|-----------------|-----------------|
| Adverse Reaction | N > 54 Subjects (Patients) | N > 40 Volunteers |
| Nausea | 1 (1) | 1 (1) |
| Early removal of feeding tube | 1 (1) | 1 (1) |
| Vomiting | 1 (1) | 1 (1) |
| Increased heart rate | 1 (1) | 1 (1) |
| Diaphoresis | 1 (1) | 1 (1) |
| Hypotension | 1 (1) | 1 (1) |
| Headache | 3 (3) | 3 (3) |
| Chills | 2 (2) | 2 (2) |
| Palpitations | 5 (5) | 5 (5) |
| Unrelated | 9 (9) | 9 (9) |

Of the 546 patients and healthy volunteers treated with ChiRhoStim®, a total of 29 patients (5%) had at least one adverse reaction.

2. DRUG INTERACTIONS

The concomitant use of antiarrhythmic agents may make patients hyporesponsive to secretin stimulation and may produce a false result. Any results of secretin stimulation tests in these studies should thus be interpreted with caution.

3. USE IN SPECIFIC POPULATIONS

3.1 Pregnancy

Animal reproduction studies have not been conducted with synthetic human secretin. It is not known whether synthetic human secretin, a hormone, crosses the placenta and is administered to a pregnant woman or can affect reproductive capacity. Synthetic human secretin should be given to a pregnant woman only if clearly needed.

3.2 Nursing Mothers

It is not known whether synthetic human secretin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when synthetic human secretin is administered to a nursing woman.

3.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

3.5 Geriatric Use

Among the 533 patients who have received ChiRhoStim® in clinical trials, 16% were 65 years of age or older, and 7% were 75 years of age or older. Dosing was the same as for the younger patients. The distribution of adverse events, laboratory abnormalities, and clinical adverse reactions between these groups showed no significant differences. difficile in the elderly patient population and for other elderly patients, but greater sensitivity of some elderly patients (5%) had at least one adverse reaction.

4. CLINICAL STUDIES

ChiRhoStim® administered intravenously stimulates the secretion of gastric juice, which can assist in the diagnosis of gastric and duodenal disease. In a three way crossover study of 14 healthy volunteers treated with ChiRhoStim, both peak bicarbonate concentration and the area under the peak bicarbonate concentration was significantly different from the control and placebo conditions.

The values obtained for Figure 1 and 2 were performed by investigators skilled in performing secretin stimulation testing and are to be taken only as guidelines. These results should not be generated in secretin stimulation testing conducted in other laboratories. However, a volume response of less than 2 mL/kg/hr, bicarbonate concentration of less than 15 mEq/L, and a bicarbonate output of less than 0.5 mL/kg/hr are consistent with impaired pancreatic function. A physician or institution planning to perform secretin stimulation testing as an aid to the diagnosis of chronic pancreatitis should be aware of the results of these studies.

The primary action of ChiRhoStim® is to increase the volume and bicarbonate content of secreted pancreatic juice. The standard unit of activity used for ChiRhoStim® is the chronic pancreatitis unit (CPU) and is defined as the amount of synthetic human secretin that stimulates a volume response of 2 mL/kg/hr and a bicarbonate response of 20 mEq/L/hr in a normal fasting healthy volunteer. ChiRhoStim® administered intravenously stimulates gastric juice secretion in patients with chronic pancreatitis. In these studies, the peak bicarbonate concentration, the area under the peak bicarbonate concentration, and the mean total volume of output were significantly different from the control and placebo conditions.

In a three way crossover study of 14 patients with tissue diagnosed gastrinoma, there was a significant increase in serum gastrin concentrations in patients treated with ChiRhoStim and a significant decrease in gastrin concentrations in patients treated with placebo. This response was significantly different from the control and placebo conditions.

When secretin binds to secretin receptors on pancreatic duct cells as a cyclic triphosphate, secretion of bicarbonate and water occurs immediately. Bicarbonate and water are released into the ductal system and subsequently into the duodenal lumen. Secretin also promotes sodium, chloride, and bicarbonate secretion into the ductal system. Secretin stimulates secretion into the ductal system by stimulating the release of other hormones, which in turn stimulate secretion into the ductal system. Secretin also stimulates secretion into the ductal system by increasing the permeability of the ductal system to calcium and other ions.

The PK profile for synthetic human secretin was evaluated in 12 normal subjects. After intravenous bolus administration of 0.4 mg/kg, synthetic human secretin concentration rapidly declined to baseline levels within 90-120 minutes. Normalization half-life of synthetic human secretin is 45 minutes. The clearance of synthetic human secretin is 0.5 mL/kg/min and the volume of distribution is 2.7 L.

The results of these studies suggest that synthetic human secretin can be used as a provocative test in the evaluation of patients in whom gastrinoma is suspected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of synthetic human secretin. Studies to evaluate the potential for impairment of fertility or maldevelopment of synthetic human secretin have not been performed.

13.2 Animal Toxicology and/or Pharmacology

A single intravenous dose of synthetic human secretin at 20 mg/kg was nontoxic to rats or mice.

14 CLINICAL STUDIES

14.1 Stimulation of pancreatic secretions, including bile, in patients with pancreatic disease.
Facilitation of identification of the ampulla of Vater and the accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP) to assist in cannulation of the pancreatic ducts

In a randomized, placebo-controlled crossover study in 24 patients with pancreas divisum undergoing ERCP, synthetic human secretin administration at a dose of 0.2 mcg/kg resulted in 16 of 24 successful cannulations of the minor duct compared to 2 of 24 for placebo.

References

How Supplied/Storage and Handling
ChiRhoStim® 16 mcg vial NDC # 87866-005-01
ChiRhoStim® 40 mcg vial NDC # 87866-007-01

16.1 Supplied
ChiRhoStim® is supplied in two strengths:
As a lyophilized sterile powder in vials containing 16 mcg of human secretin.
As a lyophilized sterile powder in vials containing 40 mcg of human secretin.

16.2 Storage
The unconstituted product should be stored at -20°C (freeze). The expiration date is marked on the label. Protect from light.

17. Patient Counseling Information
Since there is no data on pregnant or nursing mothers, physicians should discuss these matters with the patient before using this product.