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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-256

Approved Labeling

Package Insert

TRADENAME
(Human secretin) for Injection

Package Insert

DESCRIPTION

Human secretin is a gastrointestinal peptide hormone produced by cells in the duodenum in response to acidification. Human secretin (as the acetate) is a purified synthetic peptide with an amino acid sequence identical to the naturally occurring hormone. Synthetic human secretin is chemically defined as follows:

Molecular Weight 3039.44
Empirical Formula: $C_{130}H_{220}N_{44}O_{39}$
CAS # 108153-74-8

Structural Formula:
His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-Glu-Gly-Ala-Arg-Leu-Gln-Arg-Leu-Leu-Gln-Gly-Leu-Val-NH_2

TRADENAME contains 16 mcg of purified synthetic human secretin, 1.5 mg of L-cysteine hydrochloride, 20 mg of mannitol, and 0.9 mg of sodium chloride per vial. When reconstituted in 8 mL of Sodium Chloride Injection USP, each mL of solution contains 2 mcg synthetic human secretin for intravenous use. The pH of the reconstituted solution has a range of 3 to 6.5.

CLINICAL PHARMACOLOGY

The primary action of TRADENAME is to increase the volume and bicarbonate content of secreted pancreatic juices. The standard unit of activity used for TRADENAME is the clinical unit as defined in the literature[1]. Synthetic human secretin (sHS), synthetic porcine secretin (sPS) and biologically derived porcine secretin (bPS) have been evaluated and compared in the validated cat bioassay used for release of bPS. sHS and sPS were found to have similar pharmacological activity in terms of stimulating the exocrine pancreas to secrete juice and bicarbonate. The potency correlation with bPS for both sHS and sPS was 0.2 mcg (sHS or sPS) corresponding to 1 CU (bPS). The biological activity of sHS and sPS was approximately 5000 CU per mg as opposed to 3000 CU per mg for bPS.

Pharmacokinetics:

The PK profile for synthetic human secretin was evaluated in 12 normal subjects. After intravenous bolus administration of 0.4 mcg/kg, synthetic human secretin concentration rapidly declines to baseline secretin levels within 90 to 120 minutes. The elimination half-life of synthetic human secretin is 45 minutes. The clearance of synthetic human secretin is 580.9 ± 51.3 mL/min and the volume of distribution is 2.7 L.

CLINICAL STUDIES

Stimulation of pancreatic secretions, including bicarbonate to aid in the diagnosis of Exocrine Pancreas Dysfunction:

TRADENAME administered intravenously stimulates the exocrine pancreas to secrete pancreatic juice, which can assist in the diagnosis of exocrine pancreas 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 crossover studies, (CRC 98-2 and CRC 99-9), a total of 18 patients with a documented history of chronic pancreatitis were given sHS, sPS and bPS. The results appear in Figures 1 and 2. In another study, 35 normal volunteers were given sHS. The results appear in Figures 1 and 2.

FIGURE 1

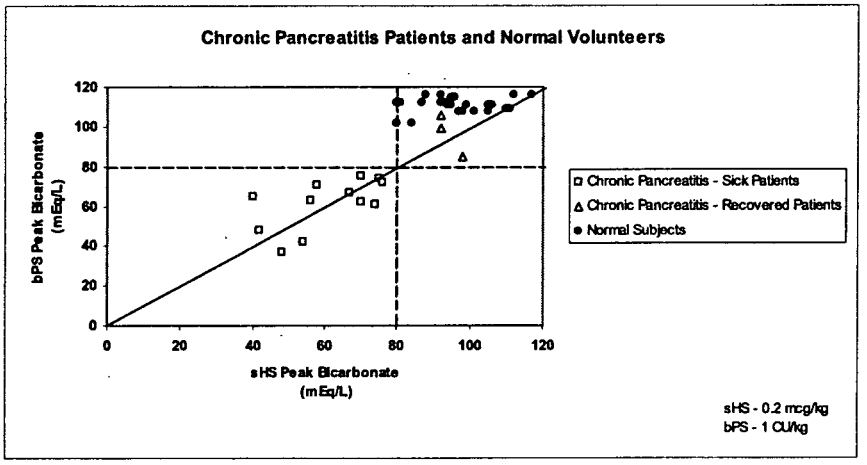
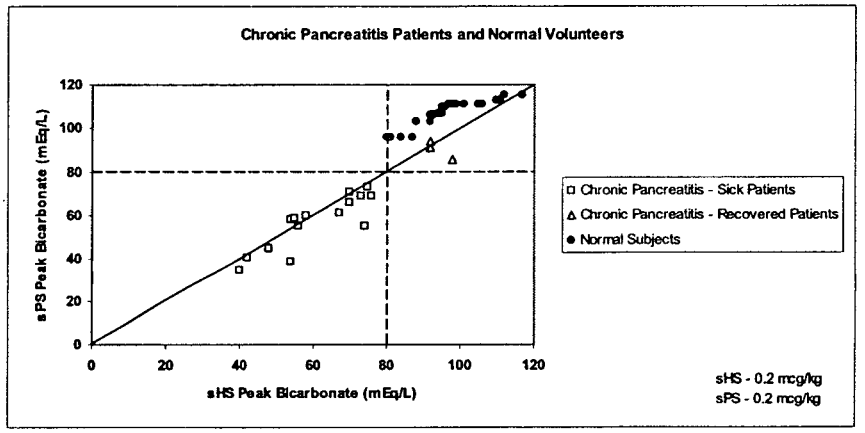


FIGURE 2



The values obtained for Figures 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 generalized to results of secretin stimulation testing conducted in other laboratories. However, a volume response of less than 2.0 mL/kg/hr, bicarbonate concentration of less than 80 mEq/L, and a bicarbonate output of less than 0.2 mEq/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 pancreatic disease should begin by assessing enough normal subjects (>5) to develop proficiency in proper techniques and to generate normal response ranges for the commonly assessed parameters for pancreatic exocrine response to TRADENAME.

In three crossover studies (CRC 98-1, CRC 98-2, and CRC 99-9) evaluating 21 different patients with a documented history of chronic pancreatitis, TRADENAME was compared to synthetic porcine secretin (sPS) and biologically derived secretin (bPS). All of the patients, treated with these drugs, had peak bicarbonate concentrations of < 80 mEq/L.

Pancreatic secretory response to intravenous human secretin in 35 normal healthy subjects demonstrated a mean peak bicarbonate concentration of 100 mEq/L and a mean total volume over one hour of 260.7 mL. All 35 subjects had peak bicarbonate concentrations ≥ 80 mEq/L.

Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma:

TRADENAME administered intravenously stimulates gastrin release in patients with gastrinoma (Zollinger-Ellison Syndrome), whereas no or only small changes in serum gastrin concentrations occur in normal subjects and in patients with duodenal ulcer disease. Deveney, et al. established the high sensitivity and specificity of the secretin stimulation test to aid in the diagnosis of gastrinoma and found using discriminate analysis that an increase from baseline of ≥ 110 pg/mL was the optimal point separating positive and negative tests. [2] This gastrin response is the basis for the use of human secretin as a provocative test in the evaluation of patients in whom gastrinoma is a diagnostic consideration.

In a three way crossover study of 6 patients with tissue diagnosed gastrinoma, there was agreement among synthetic human secretin, synthetic porcine secretin and biologically derived porcine secretin regarding gastrin levels. Serum gastrin levels were reported to be >110 pg/mL for all secretin products tested after stimulation with 0.4 mcg/kg secretin. Testing of TRADENAME in 12 healthy volunteers demonstrated completely negative results for gastrinoma.

Facilitation of identification of the ampulla of Vater and the accessory papilla during ERCP to assist in cannulation of the pancreatic ducts:

In a randomized, placebo controlled crossover study in 24 patients with pancreas divisum undergoing ERCP, sHS 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.

INDICATIONS AND USAGE

TRADENAME is indicated for:
(1) Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction,

(2) Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma, and

(3) STIMULATION OF PANCREATIC SECRETIONS TO FACILITATE THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP).

See DOSAGE AND ADMINISTRATION Section for proper methodologies for performing the secretin pancreatic stimulation test as well as its use to facilitate identification of the pancreatic duct papillae and gastrin stimulation test.

CONTRAINDICATIONS

Patients suffering from acute pancreatitis should not receive TRADENAME until the acute episode has subsided.

WARNINGS

Because of a potential allergic reaction to TRADENAME, patients should receive an intravenous test dose of 0.2 mcg (0.1 mL). If no allergic reaction is noted after one minute, the recommended dose may be injected slowly over 1 minute. A test dose is especially important in patients with a history of atopic allergy and/or asthma. Appropriate measures for the treatment of acute hypersensitivity reactions should be immediately available. No allergic reactions were observed after the test dose or full dose of sHS in 584 patients and volunteers.

PRECAUTIONS

General: Patients who have undergone vagotomy, or are receiving anticholinergic agents at the time of secretin stimulation testing, or who have inflammatory bowel disease may be hyporesponsive to secretin stimulation. This response does not indicate pancreatic disease. A greater than normal volume response to secretin stimulation, which may mask coexisting pancreatic disease, is occasionally encountered in patients with alcoholic or other liver disease.

Drug/Laboratory Test Interaction:

The concomitant use of anticholinergic agents may make patients hyporesponsive, i.e., may produce a false positive result.

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 mutagenicity of synthetic human secretin have not been performed.

Pregnancy, Teratogenic Effects, Pregnancy Category C: Animal reproduction studies have not been conducted with synthetic human secretin. It is also not known whether synthetic human secretin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Synthetic human secretin should be given to a pregnant woman only if clearly needed.

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.

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

Geriatric Use: Among the 533 patients who have received TRADENAME in clinical trials 18% were 65 years of age or older and 6% were 75 years of age or older. Dosing was the same as that of the overall population of patients. No overall differences in safety, pharmacological response, or diagnostic effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and the younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Mild to moderate adverse events have been noted for sHS in clinical studies in 533 patients and 51 healthy volunteers. Two severe adverse events, nausea and abdominal pain, occurred in one patient. Table 1 details the type and number of patients with adverse events.

TABLE 1
PATIENTS WITH ADVERSE EVENTS WITH TRADENAME

Parameter	N = 584 Incidence (Patients)
Nausea	11 (11)
Flushing	4 (4)
Early removal of Dreiling tube	3 (3)
Abdominal pain	3 (3)
Vomiting	3 (3)
Increased heart rate	2 (2)
Mild Pancreatitis	2 (2)
Upset stomach	2 (2)
Anxiety	1 (1)
Burning in stomach or abdomen	1 (1)
Clammy skin	1 (1)
Decreased O_2 saturation	1 (1)
Diarrhea	1 (1)
Faintness	1 (1)
Hypotension	1 (1)
Infiltrated IV	1 (1)
Oral secretions increased	1 (1)
Sedation	1 (1)
Slow heart rate (57bpm)	1 (1)
Tingling in legs	1 (1)
Unresponsive	1 (1)
Warm sensation in abdomen	1 (1)
Warm sensation in face	1 (1)

Of the 584 patients and healthy volunteers treated with TRADENAME, a total of 29 patients (5.0%) had at least one adverse event.

OVERDOSAGE

A single intravenous dose of synthetic human secretin at 20 mcg/kg was not lethal to mice or rabbits.

DOSAGE AND ADMINISTRATION

Dissolve the contents of the vial in 8 mL of Sodium Chloride Injection USP, to yield a concentration of 2 mcg/mL. Shake vigorously to ensure dissolution. Use immediately after reconstitution. Discard any unused portion after reconstitution.

The reconstituted drug product should be inspected visually prior to administration. If particulate matter or discoloration is seen, the product should be discarded.

Dosage

SECRETIN STIMULATION TESTING:

1. STIMULATION OF PANCREATIC SECRETIONS INCLUDING BICARBONATE TO AID IN THE DIAGNOSIS OF EXOCRINE PANCREAS DYSFUNCTION: 0.2 mcg/kg body weight by intravenous injection over 1 minute.

2. STIMULATION OF GASTRIN SECRETION TO AID IN DIAGNOSIS OF GASTRINOMA: 0.4 mcg/kg body weight by intravenous injection over 1 minute.

3. FACILITATION OF THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ERCP to aid in cannulation of the pancreatic duct: 0.2 mcg/kg body weight by intravenous injection over 1 minute.

Administration

SECRETIN STIMULATION TESTING:

1. STIMULATION OF PANCREATIC SECRETIONS, INCLUDING BICARBONATE TO AID IN THE DIAGNOSIS OF EXOCRINE PANCREAS DYSFUNCTION: A radiopaque, double-lumen tube is passed through the mouth following a 12-15 hour fast. 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 positioning of the tube must be confirmed and the tube secured prior to human secretin testing.

Intermittent negative pressure of 25-40 mmHg is applied to both lumens and maintained throughout the test. When duodenal contents have a pH of ≥ 6.0, a baseline sample of duodenal fluids is collected for a 10 minute period. A test dose of TRADENAME 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies. After one minute, if there are no untoward reactions, TRADENAME at a dose of 0.2 mcg/kg of body weight is injected intravenously over 1 minute. Duodenal fluid is collected for 60 minutes thereafter. The aspirate is divided into four collection periods of fifteen minutes each. The duodenal lumen of the tube is cleared with an injection of air after collection of each sample. Wide variation in volume of the aspirate is indicative of incomplete aspiration. Each sample of duodenal fluid is to be chilled and subsequently analyzed for volume and bicarbonate concentration. Exocrine pancreas dysfunction typically associated with chronic pancreatitis is indicated if the peak bicarbonate concentration for any sample ≤ 80 mEq/L.

2. STIMULATION OF GASTRIN TO AID IN THE DIAGNOSIS OF GASTRINOMA: The patient should have fasted for at least 12 hours prior to beginning the test. Prior to injection of TRADENAME, two blood samples are drawn for determination of fasting serum gastrin levels (baseline values). Subsequently, a test dose of TRADENAME 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies. If no untoward reactions, TRADENAME at a dose of 0.4 mcg/kg of body weight is injected intravenously over 1 minute; post-injection blood samples are collected after 1, 2, 5, 10, and 30 minutes for determination of serum gastrin concentrations.

Gastrinoma is strongly indicated in patients who show an increase in serum gastrin concentrations in the 110 pg/mL over basal level on any of the post injection samples.

3. FACILITATION OF THE IDENTIFICATION OF THE AMPULLA OF VATER AND ACCESSORY PAPILLA DURING ERCP: Administration of TRADENAME may be given when difficulty is encountered by the endoscopist in identifying the ampulla of Vater for reasons including anatomic deformity secondary to prior surgery, radiation therapy, peptic ulcer disease, tumors, etc. or in identifying the accessory papilla in patients with pancreas divisum. A test dose of TRADENAME 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies. A dose of 0.2 mcg/kg of body weight intravenously over 1 minute will result in visible excretion of pancreatic fluid from the orifices of these papillae enabling their identification and facilitating cannulation.

HOW SUPPLIED

TRADENAME is supplied as a lyophilized sterile powder in vials containing 16 mcg.

STORAGE: The unreconstituted product should be stored at -20°C (freezer). Expiration date is marked on the label. Protect from light.

RX only

References

1. Jorpes, E. and Mutt V.
On the biological assay of secretin. The reference standard.
Acta Physiol Scand 66 (1966) 316-325.
2. Deveney, C.W., et al.
Use of Calcium and Secretin in the Diagnosis of Gastrinoma (Zollinger-Ellison Syndrome).
Annals of Internal Medicine 87 (1977) 680-686.

TRADENAME is a registered trademark of ChiRhoClin, Inc.
Manufactured for:
ChiRhoClin, Inc
Burtonsville, MD 20866-6129

by:
Bell-More Laboratories, Inc.
Hampstead, Maryland 21074-0179

April 5, 2004

ChiRhoClinPI205

Draft Vial Label

NDC-67066-002-01

Tradename
(human secretin)
for Injection
16 mcg

For Intravenous Use Only. For Single Use Only.

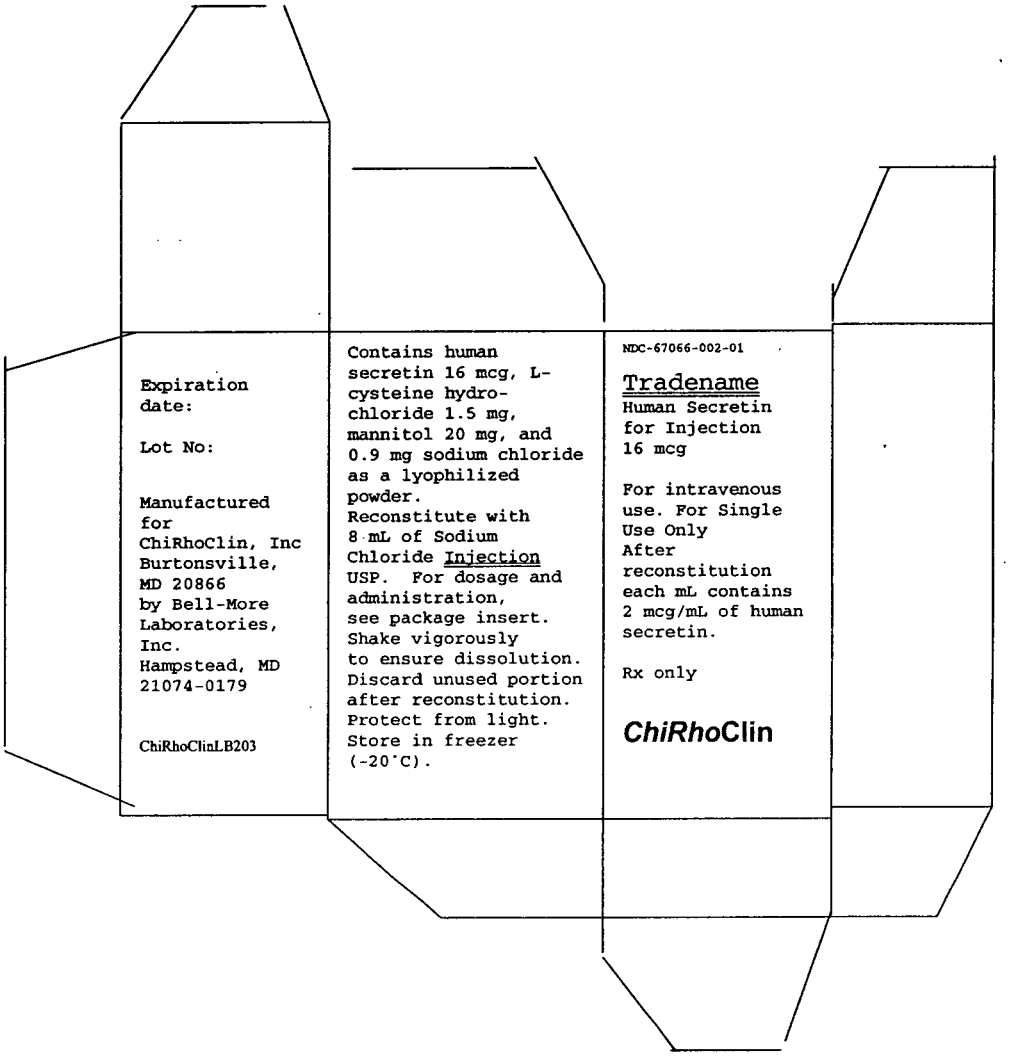
Rx only

***ChiRho*Clin**

Vial contains human secretin 16 mcg, L-cysteine hydrochloride 1.5 mg, mannitol 20 mg, and sodium chloride 0.9 mg as a lyophilized powder.
For reconstitution, dosage and administration, see package insert.
Reconstitute with 8 mL Sodium Chloride ~~for~~ Injection USP. Use immediately after reconstitution. Discard unused portion after reconstitution.
Protect from light.
Store in freezer (-20°C).
Manufactured for ChiRhoClin, Inc.
Burtonsville, MD 20866-6129
By Bell-More Laboratories
Hampstead, MD 21074-0179
ChiRhoClinLV203

Expiration date:
Lot No:

Draft Box Label



Expiration date:

Lot No:

Manufactured for ChiRhoClin, Inc Burtonsville, MD 20866 by Bell-More Laboratories, Inc. Hampstead, MD 21074-0179

ChiRhoClinLB203

Contains human secretin 16 mcg, L-cysteine hydrochloride 1.5 mg, mannitol 20 mg, and 0.9 mg sodium chloride as a lyophilized powder. Reconstitute with 8 mL of Sodium Chloride Injection USP. For dosage and administration, see package insert. Shake vigorously to ensure dissolution. Discard unused portion after reconstitution. Protect from light. Store in freezer (-20°C).

NDC-67066-002-01

Tradename
Human Secretin for Injection
16 mcg

For intravenous use. For Single Use Only
After reconstitution each mL contains 2 mcg/mL of human secretin.

Rx only

*ChiRho*Clin