CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-136

21-209

APPROVED LABELING

SecreFlo™
(secretin) for Injection

DESCRIPTION

SecreFlo™ (secretin) is a pure sterile, nonpyrogenic, lyophilized white cake powder acetate salt of secretin, a peptide hormone. Secretin has an amino acid sequence identical to the naturally occurring porcine secretin consisting of 27 amino acids. Secretin is chemically defined as follows:

Molecular Weight 3055.5
Empirical Formula: $C_{130}H_{220}N_{44}O_{41}$

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

SecreFlo contains 16 mcg of purified secretin, 15 mg of L-cysteine hydrochloride, and 20 mg of mannitol per vial. When reconstituted in 8 mL of Sodium Chloride Injection USP, each mL of solution contains 2 mcg secretin for intravenous use. The pH of the reconstituted solution has a range of 3-6.5.

CLINICAL PHARMACOLGY

The primary action of SecreFlo is to increase the volume and bicarbonate content of secreted pancreatic juices. The standard unit of activity used for SecreFlo is the clinical unit defined by Jorpes & Mutt in 1966. [1] In the validated cat bioassay, which was used to define and quantitate the biological activity of secretin and as the release test for the biologically derived porcine secretin product, SecreFlo™ demonstrates a potency of approximately 5000 clinical units (CU) per milligram of peptide as opposed to 3000 CU per mg for biologically derived porcine secretin. As a pure peptide drug product, SecreFlo™ dosing is expressed by weight in micrograms. The relationship of micrograms of secretin to biological activity is 0.2 mcg = 1 CU.

Pharmacokinetics:

The PK profile for SecreFlo™ was evaluated in 12 normal subjects. After intravenous bolus administration of 0.4 mcg/kg, SecreFlo™ concentration rapidly declines to baseline secretin levels within 60 to 90 minutes in most of the normal volunteers studied. The elimination half-life of SecreFlo™ is 27 minutes. The clearance of SecreFlo™ is 487 ± 136 mL/minute and the volume of distribution is about 2 liter.

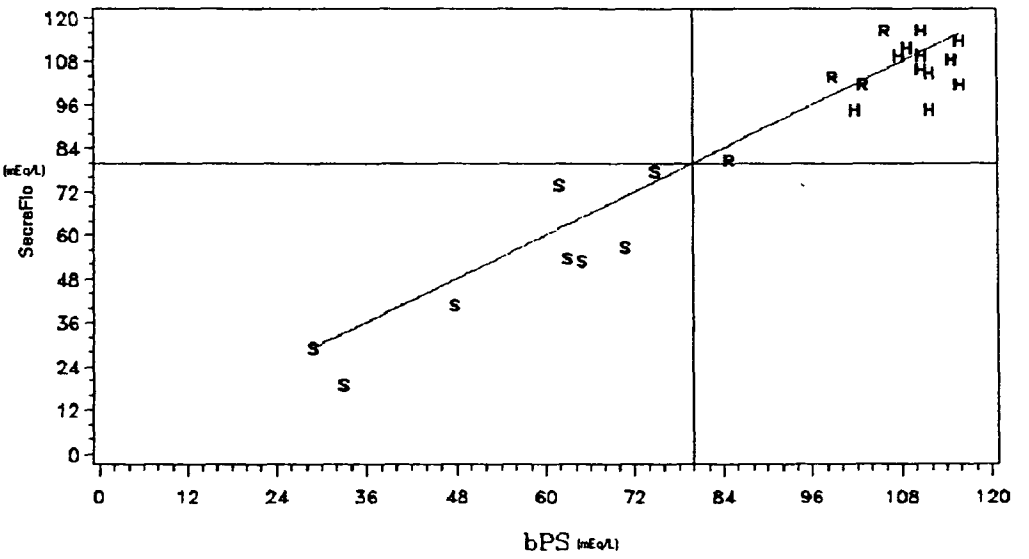
CLINICAL STUDIES

To stimulate pancreatic secretions, including bicarbonate, to aid in the diagnosis of exocrine pancreas dysfunction:

SecreFlo 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 diseases have been shown to vary. One source of variation is related to the inter-investigator differences in operative technique. Two small studies (CRC 97-1 and CRC 98-1) examined the relationship of peak bicarbonate concentration observed in three groups of patients: normal health subjects; patients with chronic pancreatitis; patients with a past medical history of chronic pancreatitis and abnormal secretin stimulation test results but with sufficient recovery of exocrine pancreas function to have currently normal test results (Fig 1). SecreFlo was compared to biologically derived porcine secreting (bPS). All 12 normal subjects had peak bicarbonate concentrations > 80 mEq/L while all patients with chronic pancreatitis had peak bicarbonate concentrations < 80 mEq/L.

Figure 1.

PEAK BICARBONATE FROM STUDIES 97_1 & 98_1



A 45 DEGREE REFREENCE LINE: bPS = SecreFlo
S: SICK PATIENTS;
R: RECOVERED PATIENTS;
H: HEALTHY SUBJECTS.

The values obtained for Figure 1 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 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 for 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 of pancreatic exocrine response to SecreFlo.

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, SecreFlo™, was compared to biologically derived porcine secreting (bPS). All of the patients, treated with either drug, had peak concentrations of < 80 mEq/L.

Proper technique for carrying out secretin stimulation testing is described in DOSAGE AND ADMINISTRATION.

Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma:
SecreFlo administered intravenously stimulates gastrin release in patients with gastrinoma whereas only small changes in serum gastrin concentrations occur in normal subjects and patients with peptic ulcer disease. Deveney et al.[(2)] established secretin stimulation testing as an aid in the diagnosis of gastrinoma by using discriminant analysis. An increase from basal levels of ≥ 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 two crossover studies, eight patients with tissue confirmed gastrinoma received SecreFlo. Results of serum gastrin concentrations were compared with those for biologically derived porcine secretin. Serum gastrin concentrations exceeded 100 pg/mL from basal levels in all patients for both drugs tested.

Correlation with clinical data and additional diagnostic modalities should be utilized when considering the diagnosis of gastrinoma.

Proper technique for carrying out secretin stimulation testing is described in DOSAGE AND ADMINISTRATION.

INDICATIONS AND USAGE

SecreFlo™ is indicated for use in secretin stimulation testing 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.

CONTRAINDICATIONS

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

WARNINGS

Because of a potential allergic reaction to secretin, 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 for the specific indication (see DOSAGE AND ADMINISTRATION) 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 SecreFlo™ in over 556 patients.

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 secretin. Studies to evaluate its potential for impairment of fertility or its mutagenic potential have not been established.

Pregnancy. Teratogenic Effects. Pregnancy Category C: Animal reproduction studies have not been conducted with secretin. It is also not known whether secretin can cause fetal

harm when administered to a pregnant woman or can affect reproduction capacity. Secretin should be given to a pregnant woman only if clearly needed.

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

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

Geriatric Use: Among the 556 patients who have received SecreFlo™ in clinical trials 16% were 65 years of age or older and 12% were 75 years of age or older. Dosing was identical to the overall population of patients. No overall differences in safety, pharmacological response, or diagnostic effectiveness were observed between these subjects and younger subjects, and 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

Occasional mild adverse events have been noted in association with the use of SecreFlo™ in clinical studies of over 556 patients and 24 volunteer subjects.

Table 4
Adverse Events

Event	SecreFlo N = 556 Incidence (Patients)
Abdominal cramps	1 (1)
Abdominal discomfort	6 (5)
Bleeding-sphincterectomy	2 (2)
Bleeding-upper GI 2° to endoscopic abrasion	1 (1)
Bloating	1 (1)
Bradycardia (mild)	2 (2)
Decreased blood pressure	2 (2)
Diaphoresis	2 (2)
Diarrhea	1 (1)
Endoscopic perforation of pancreatic duct	2 (2)
Fever	1 (1)
Nausea	5 (5)
Transient low O^2 saturation	1 (1)
Transient respiratory distress	1 (1)
Urticaria 2° contrast material (prior to secretin administration)	1 (1)
Vomiting	1 (1)
Total patients with AEs (%)	29 (5.2)

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Dissolve the contents of a vial of SecreFlo in 8 mL of Sodium Chloride Injection USP, to yeild 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. TO STIMULATE PANCREATIC SECRETIONS, INCLUDING BICARBONATE, TO AID IN THE DIAGNOSIS OF EXOCRINE PANCREATIC DYSFUNCTION: 0.2 mcg/kg body weight by intravenous injection over 1 minute.

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

Administration

SECRETIN STIMULATION TESTING:
1. TO STIMULATE 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 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 $\geq$ 6.0, a baseline sample of duodenal fluids is collected for a 10 minute period. A test dose of SecreFlo 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies. After one minute, if there are no untoward reactions, SecreFlo 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 is <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. Before injecting SecreFlo, two blood samples are drawn for determination of fasting serum gastrin levels (baseline values). Subsequently, a test dose of SecreFlo 0.2 mcg (0.1 mL) is injected intravenously, to test for possible allergies If no untoward reactions, 0.4 mcg/kg of SecreFlo is administered 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 suspected in patients who show an increase in serum gastrin concentration of more than 110 pg per mL over basal levels on any of the post injection samples.

HOW SUPPLIED

SecreFlo™ is supplied as a lyophilized sterile powder in vials containing 16 mcg secretin.

STORAGE: The unreconstituted product should be stored at -20°C (freezer).

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.

Manufactured for:
***Repli*Gen Corporation**
Needham, MA 02494
by:
Chesapeake Biological Laboratories
Baltimore, MD 21230

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/s/

Joyce Korvick
4/4/02 03:54:54 PM
for Dr. Victor Raczkowski