

## 1. NAME OF THE MEDICINAL PRODUCT

Secretine Iberoinvesa Pharma S.L. 100 E, poeder en oplosmiddel voor oplossing voor injectie/infusie

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: secretin pentahydrochloride

One vial with 24.4 mg powder contains 0.029 mg secretin pentahydrochloride, equivalent to the effect of 100 clinical units (CU).

The biological activity of this completely synthetic active constituent is equivalent to that of porcine secretin.

One vial with 10 ml solvent contains sodium chloride 9 mg/ml (0.9 %) solution for injection

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.

1 vial with 24.4 mg powder (white to off-white freeze-dried pellet that may break into powder) (= 100 CU) and 1 vial with 10 ml solvent (clear colourless solution).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Secretin Iberoinvesa Pharma is indicated in adults for the following:

- Diagnosis of exocrine pancreatic dysfunction
- Diagnosis of Zollinger-Ellison-Syndrome

### 4.2 Posology and method of administration

#### Posology:

For diagnosis of exocrine pancreatic dysfunction: 1 CU secretin/kg body weight

Diagnosis of Zollinger-Ellison syndrome: 2 CU secretin/kg body weight

#### Method of administration:

The solution for injection is to be injected or infused intravenously depending on the nature of the test.

In general, Secretin Iberoinvesa Pharma should only be administered once.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

#### ***Diagnosis of exocrine pancreatic conditions***

#### Posology:

Secretin Iberoinvesa Pharma can be used as follows for the diagnosis of exocrine pancreatic dysfunction.

#### Method of administration:

Dissolve Secretin Iberoinvesa Pharma in 10 ml sodium chloride 9 mg/ml (0.9 %) solution for injection.

Inject 1 CU secretin/kg body weight intravenously over 1 – 2 minutes or infuse intravenously over up to 1 hour. Use the freshly prepared solution immediately.

When Secretin Iberoinvesa Pharma is used in combination with pancreozymin or caerulein, it is recommended that the investigation be started with intravenous injection of Secretin Iberoinvesa Pharma (1 CU/kg body weight). After 1 hour, Secretin Iberoinvesa Pharma should be infused - if necessary - at a

dosage of 1 CU/kg body weight per hour (infusion duration 1 hour), with simultaneous administration of pancreozymin or caerulein.

Conduct and evaluation:

After fasting the patient for 10 – 12 hours introduce a double-lumen (Lagerlöf) or triple-lumen (Bartelheimer) radiodense indwelling tube through the mouth or the nose, so that one tube opening is in the fundus of stomach and the other in the distal third of the duodenum. Discard the duodenal juice obtained at the start and the stomach contents obtained throughout the test. Following this, aspirate duodenal juice over a 20-minute collection period and collect in an ice-cooled vessel. Use this sample to determine the baseline values. After intravenous administration of Secretin Iberoinvesa Pharma, collect secretions at intervals of 20 minutes for 1 hour.

Secretin Iberoinvesa Pharma (1 CU/kg body weight per hour) and pancreozymin may then be administered slowly intravenously. In this case, continue the collection of secretion for 1 hour in three 20-minute periods. Reflux of duodenal secretion into the stomach or loss of secretion into the distal small intestine can distort the result of the test. Simultaneous continuous administration of a marker into the duodenum over this period allows calculation of the secretion rate by calculation of the recovery rate.

Normal values:

After i.v. injection of 1 CU/kg body weight Secretin Iberoinvesa Pharma causes secretion in healthy subjects of 2 – 5 ml pancreatic juice/min with a bicarbonate concentration of 80 - 150 mmol/L with a minimum of 70 mmol/L. This corresponds to a bicarbonate production rate of 160 – 750 µmol/min.

Values relating to an overall collection period of 1 hour after intravenous administration of Secretin Iberoinvesa Pharma are given in Table 1 below.

**Table 1: Pancreatic secretory response to synthetic porcine secretin in healthy volunteers**

	Median	Range
Volume/60 min (ml)	242	173 - 304
HCO <sub>3</sub> output/60 min (mmol)	22.2	15.5 - 34.3
Protein output/60 min (g)	3.3	2.31 - 6.0
Amylase output/60 min (KU)	25.0	12.4 - 47.1

Data from [Beglinger et al., 1982](#).

Evaluation:

Functional disturbances of the pancreas, such as occur in chronic pancreatitis, chronic calcifying pancreatitis, or pancreatic carcinoma, can cause changes in the volumes and bicarbonate secretion in a manner determined by the site, nature and extent of the disease. The measured variables can also vary independently of each other, so that abnormal values generally only indicate pancreatic disease, but the results of the test do not permit firm conclusions concerning the nature and severity of the disease. Threshold values for volume response of < 2.0 mL/kg/hr, bicarbonate concentration of < 80 mmol/L, and bicarbonate output of < 0.2 mmol/kg/hr are consistent with impaired pancreatic function. If necessary, pancreatic function tests may be repeated after 2 – 3 days.

**Diagnosis of Zollinger-Ellison syndrome**

Posology:

For diagnosis of Zollinger-Ellison syndrome the secretin-gastrin-test as described below can be used.

Method of administration:

For this test, the following procedure is recommended:

- Take 2 baseline blood samples from the fasting patient (10 – 12 hours) at 15-minute intervals
- i.v. injection of 2 CU secretin/kg body weight as bolus (over 30 seconds)
- Take blood 2, 5, 10, 15 and 30 minutes after secretine injection.

Evaluation of the secretin-gastrin-test in Zollinger-Ellison syndrome

Baseline values for serum gastrin in patients with Zollinger-Ellison syndrome are usually greater than those of control subjects to varying degrees.

In principle, a transient, clearly "paradoxical" rise of the serum gastrin level of more than 120 pg/ml after i.v. administration of 2 CU secretin/kg body weight is taken as evidence of the presence of Zollinger-Ellison syndrome.

If necessary, pancreatic function tests may be repeated after 2 – 3 days, particularly for diagnosis of Zollinger-Ellison syndrome.

Due to possible distortion of test results it should be considered to discontinue proton pump inhibitors before the secretin-gastrin-test, if this is medically justifiable (see also section 4.5).

#### *Renal or hepatic impairment*

No studies have been conducted in patients with renal or hepatic impairment. Because secretin is in part eliminated via the kidney, and does itself exert diuretic and saluretic effects, patients with renal and hepatic impairment should generally be treated with caution. The treatment of patients with moderate or severe renal impairment is not recommended (see also chapter 4.4.).

#### *Paediatric population*

The safety and efficacy of Secretin Iberoinvesa Pharma in the paediatric population has not been established.

Until relevant experience is available, no recommendation on a posology of Secretin Iberoinvesa Pharma in the paediatric population can be made.

#### *Elderly patients*

No overall differences in safety, pharmacological response, or diagnostic effectiveness were observed between older subjects and younger subjects, and other reported clinical experience has not identified differences in responses of elderly compared to younger patients, but greater sensitivity of some older individuals cannot be ruled out. However, apart from the influence of alterations of renal function, which are more likely to affect the elderly (see also chapter 4.4.), no age specific dose adaptations are recommended.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pancreatic function testing with Secretin Iberoinvesa Pharma is contraindicated in acute pancreatitis or during an acute episode of chronic pancreatitis. The investigation should be performed at least 2 weeks after complete resolution of the acute symptoms.

### **4.4 Special warnings and precautions for use**

#### *Renal or hepatic impairment*

Secretin may exert diuretic and saluretic effects and may affect patients with electrolyte and water disturbances. Patients should therefore be well hydrated and have a good electrolyte balance before secretin is administered. Since secretin is in part eliminated via the kidney, pronounced side effects of secretin can be expected in patients with impaired renal function. The treatment of patients with moderately to severely impaired renal function is not recommended. Impaired hepatic function is not expected to have an impact on the safety profile of secretin.

#### *Severe SIADH or other electrolyte disturbances*

Due to the risk of hyponatraemia and other diuretic and saluretic effects, Secretin Iberoinvesa should be used with caution in patients with moderate or severe SIADH or other electrolyte disturbances.

#### Vasovagal reactions and transient increase of heart rate

Vasovagal reactions encompassing transient decrease of blood pressure and transient increase of heart rate have been observed with intravenous infusion and bolus injection of secretin, and could be considered as a class effect. Special care should therefore be taken when administering secretin to hypotonic patients or patients tending to vasovagal attacks.

Secretin affects the blood levels of other hormones such as rapid increase of insulin, which may cause nausea or dizziness during treatment with secretin. Special care should therefore be taken when administering secretin to hypoglycaemic, hyperinsulinaemic, or diabetic patients.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No interaction studies have been performed.

Carbonic anhydrase inhibitors, peripherally-acting synthetic anticholinergics, ACTH, corticosteroids, thyroxine, oestrogens, progesterone, prolactin, glucagon, prostaglandins, and morphine reduce the effect of secretin.

Simultaneous pancreatic investigation with Secretin and stomach secretion investigation with pentagastrin is not advisable because of the overlap in effects; the two active substance have additive blood pressure-reducing effects.

#### Influencing diagnostic tests

It should be noted in the diagnosis of Zollinger-Ellison syndrome that proton pump inhibitors as strong acid inhibitors usually cause a significant hypergastrinemia and therefore might lead to false positive results of the tests. It should therefore be considered to discontinue proton pump inhibitors at an early stage before the secretin gastrin test, if this is medically justifiable.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy:

There are no or limited amount of data from the use of synthetic porcine secretin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Secretin Iberoinvesa Pharma is not recommended during pregnancy.

##### Lactation:

It is unknown whether synthetic porcine secretin/metabolites are excreted in human milk. Secretin Iberoinvesa Pharma is not recommended during lactation.

##### Fertility:

There are no studies on the effect of Secretin Iberoinvesa Pharma on fertility.

#### **4.7 Effects on ability to drive and use machines**

Not relevant.

#### **4.8 Undesirable effects**

As other medicines, Secretin Iberoinvesa Pharma may also cause undesirable effects. Frequencies are defined as follows:

very common:	≥1/10
common:	≥1/100 to <1/10
uncommon:	≥1/1,000 to <1/100
rare:	≥1/10,000 to <1/1,000
very rare:	<1/10,000
not known:	cannot be estimated from the available data.

<b>System Organ Class</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Not known</b>
Immune system disorders				Hypersensitivity reactions against the peptide, that can express in headache, increase of blood pressure, tachycardia, pruritus, exanthema, as well as urticaria,
<b>Metabolism and nutrition disorders</b>		Electrolyte disturbance		Acidosis, Hyponatraemia, Hypocalcaemia,
<b>Nervous system disorders</b>				Vertigo (if injected too fast)
<b>Gastrointestinal disorders</b>			Diarrhea, sometimes in conjunction with abdominal cramps or nausea and retching	Increased volume of gastric fluid (during infusion of Secretin Iberoinvesa Pharma)
<b>Renal and urinary disorders</b>				Micturition urgency (during infusion of Secretin Iberoinvesa Pharma), Increased urinary volume
<b>General disorders</b>				Hot flush (if injected too fast)
<b>Investigations</b>	Pancreas enzymes increased (amylase, lipase, trypsin) in blood			Decreased blood pressure. Short-term decrease of blood sugar in diabetics
<b>Cardiac disorders</b>				Increased heart rate, faintness, hypotension, and slow heart rate.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V\\*](#).

## **4.9 Overdose**

### Symptoms

Overdoses of secretin have a blood pressure-lowering effect.

Acute poisoning with Secretin Iberoinvesa Pharma has not been reported.

Excessive dosages and long-term administration of secretin lead to longstanding secretion of pancreatic juice and bicarbonate. This can lead to disturbances of the acid-base balance and the water balance.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

#### *Pharmacotherapeutic group:*

V04           DIAGNOSTIC AGENTS  
V04CK       Tests for pancreatic function

#### *ATC code:*

V04CK01   synthetic, pork secretin.

#### *Pharmacodynamic effects*

Secretin is a hormone that is normally released from the duodenum upon exposure of the proximal intestinal lumen to gastric acid, fatty acids and amino acids. Secretin is released from enterochromaffin cells in the intestinal mucosa. Secretin receptors have been identified in the pancreas, stomach, liver, colon and other tissues.

When secretin binds to secretin receptors on pancreatic duct cells it opens cystic fibrosis transmembrane conductance regulator (CFTR) channels, leading to secretion of bicarbonate-rich-pancreatic fluid. Secretin may also work through vagal-vagal neural pathways since stimulation of the efferent vagus nerve stimulates bicarbonate secretion and atropine blocks secretin-stimulated pancreatic secretion.

Secretin Iberoinvesa Pharma causes a marked increase in pancreatic secretion and bicarbonate production lasting 1 – 2 hours. It is therefore suitable for testing the excretory function of the pancreas.

In the presence of Zollinger-Ellison syndrome, secretin leads to a “paradoxical” release of gastrin from the tumour causing the disease (gastrinoma).

#### *Clinical efficacy and safety*

#### *Diagnosis of exocrine pancreatic dysfunction*

Secretin administered intravenously stimulates the exocrine pancreas to secrete pancreatic juice, which can assist in the diagnosis of exocrine pancreas dysfunction.

Several studies using porcine secretin test have described its role in identifying patients with chronic pancreatitis.

The secretin stimulation test (SST) is considered a sensitive diagnostic test for the diagnosis of the consequences of chronic pancreatitis (CP) because it detects subtle exocrine dysfunction that accompanies early fibrosis. Lack of a reliable gold standard has hampered attempts at defining the sensitivity and specificity of PFTs for diagnosis of exocrine pancreatic function. Studies comparing PFTs with "established CP" defined as patients with advanced structural changes on imaging tests have demonstrated sensitivity ranging 72 to 94%.

The SST, when compared with histology, is 75% sensitive in detecting early stage CP, and up to 97% for late stage disease with a specificity of 90%.

The use of secretin for the diagnosis of chronic pancreatitis and other duct abnormalities of the pancreas by ultrasonography, ERCP and Magnetic Resonance Imaging has not been authorised in Europe due to overall lack of proof of sufficient visualisation enhancement and clinical usefulness.

## *Stimulation of gastrin secretion to aid in the diagnosis of Zollinger-Ellison-Syndrome (gastrinoma)*

The secretin stimulation test can differentiate between patients with gastrinoma and those with many other causes of hypergastrinemia and should be performed in every patient suspected ZES who has a nondiagnostic fasting serum gastrin concentration.

A high sensitivity and specificity of the secretin stimulation test to aid in the diagnosis of gastrinoma was established and found by using discriminant analysis that an increase from baseline of more than 120 pg/mL was the optimal point separating positive and negative tests (sensitivity of 94%, specificity 100%).

### **5.2 Pharmacokinetic properties**

Elimination:

the serum half-life is 3 - 5 minutes.

#### *Renal or hepatic impairment*

Secretin has not been systematically studied in patients with impaired hepatic or renal function. It is known that secretin may exert diuretic and saluretic effects, and may affect patients with electrolyte and water disturbances. Since secretin is in part eliminated via the kidney, pronounced side effects of secretin can be expected in patients with impaired renal function. Impaired hepatic function is not expected to have an impact on the safety profile of secretin.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

No studies on toxicity to reproduction/development and fertility are available.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Glycine hydrochloride, glycine, polygelin

### **6.2 Incompatibilities**

In the absence of compatibility studies, Secretin Iberoinvesa Pharma must not be mixed with other medicinal products except those mentioned in section 6.6.

### **6.3 Shelf life**

3 years

The freshly prepared solution must be used immediately.

### **6.4 Special precautions for storage**

Store and transport refrigerated (2°C – 8°C).

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

Keep the vials in the outer carton in order to protect from light.

## **6.5 Nature and contents of container**

The powder and solvent are filled into 15R clear glass vials (Ph.Eur., Type I) The vials are closed with bromobutyl rubber stoppers. The primary packaging material is sealed with aluminium Snap Caps with polypropylene (PP) plastic disc.

One single pack contains:

1 vial with 24.4 mg powder (= 100 CU) and  
1 vial with 10 ml solvent.

5er-bundle packs (5 × 1) contain:

5 single packs

5er-bulk packs (5 + 5) contain:

5 vials, each containing 24.4 mg of powder and  
5 vials, each containing 10 ml of solvent.

5er-combi packs (2 × 5) contain:

one pack with 5 vials each containing 24.4 mg of powder and  
one pack of 5 vials each containing 10 ml of solvent.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

The medicinal product must be reconstituted under aseptic conditions.

For reconstitution to a final concentration of 10 CU secretin per ml the full volume of solvent provided should be transferred to the vial containing the powder. The mixture should be agitated gently until complete dissolution (which, in general, occurs immediately).

The reconstituted preparation is a clear and colourless solution. Prior to administration it should be inspected visually for particles and colour.

Secretin Iberoinvesa Pharma solution for injection is administered depending on the nature of the test by intravenous injection or infusion after reconstitution of the powder only with the supplied solvent (10 ml sodium chloride 9 mg/ml (0.9 %)).

The reconstituted solution is for single use only. Any unused solution should be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

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## **8. MARKETING AUTHORISATION NUMBER(S)**

RVG 111527



**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Datum van eerste verlening van de vergunning: 11 maart 2015

**10. DATE OF REVISION OF THE TEXT**