PRODUCT MONOGRAPH

Pr SOMATULINE® AUTOGEL®

lanreotide injection
60 mg, 90 mg, 120 mg lanreotide (as acetate)/unit (syringe)

Antigrowth hormone; ATC Code: H01C B03

Sponsor:
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Deep subcutaneous injection	injection 60 mg, 90 mg, 120 mg lanreotide (as acetate) /unit (syringe)	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Somatuline® Autogel® (lanreotide) is indicated for:

- the long-term treatment of patients with acromegaly due to pituitary tumors who have had inadequate response to or cannot be treated with surgery and/or radiotherapy.
- the relief of symptoms associated with acromegaly.

The goal of treatment in acromegaly is to reduce growth hormone (GH) and age adjusted insulin-like growth factor 1 (IGF-1) levels and where possible to achieve normalization of the values.

Somatuline® Autogel® (lanreotide) is indicated for the treatment of enteropancreatic neuroendocrine tumors in patients with Grade 1 or a subset of Grade 2 (equivalent to Ki67 < 10%) unresectable, locally advanced or metastatic disease to delay progression.

- The effectiveness of Somatuline Autogel is based on a phase III placebo-controlled study which demonstrated a benefit in progression-free survival in patients classified with stable disease by RECIST criteria (<20% growth) over 12 to 24 weeks. There was no evidence of an overall survival benefit. Data on hindgut tumors were limited (see CLINICAL TRIALS).

Geriatrics (> 65 years of age):
Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in pharmacokinetics. Due to the wide therapeutic window of lanreotide, it is not necessary to adapt the dose. A brief discussion can be found in the appropriate sections (e.g. Clinical Trials, Pharmacology, Warnings and Precautions).

Pediatrics (< 16 years of age):
There is no experience of the use of the product in children and therefore the use of Somatuline Autogel in children cannot be advised.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients who are hypersensitive to somatostatin or related peptides.
- Patients with complicated, untreated lithiasis of the bile ducts

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Loss of blood glucose control (hypoglycemia in diabetic patients; hyperglycemia) can occur (see Endocrine and Metabolism section)
- Gall bladder motility may be reduced and lead to gall stone formation (see Hepatic/Biliary/Pancreatic section)
- Drug interaction with cyclosporin (see Drug Interactions section)

Cardiovascular

Lanreotide may lead to a decrease of heart rate without necessarily reaching the threshold of bradycardia in patients without an underlying cardiac problem. In patients suffering from cardiac disorders prior to lanreotide initiation, sinus bradycardia may occur and therefore heart rate should be monitored.

In 81 patients with baseline heart rates of ≥ 60 beats per minute (bpm) treated with Somatuline Autogel in enteropancreatic neuroendocrine tumors (NETs) Study 726, the incidence of heart rate < 60 bpm was 23% (19/81) as compared to 16 % (15/94) of placebo treated patients; ten patients (12%) had documented heart rates < 60 bpm on more than one visit. The incidence of documented episodes of heart rate < 50 bpm as well as the incidence of bradycardia reported as an adverse event was 1% in each treatment group. Initiate appropriate medical management in patients who develop symptomatic bradycardia.

Endocrine and Metabolism

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and its analogues, inhibits the secretion of insulin and glucagon. Hence, patients treated with Somatuline Autogel may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when lanreotide treatment is initiated or when the dose is changed and treatment of diabetic patients should be adjusted accordingly. In insulin-dependent patients, insulin requirements may be reduced.

Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, though clinical hypothyroidism is rare. Thyroid function tests are recommended where clinically indicated.

Gastrointestinal

The gastrointestinal effects of lanreotide may reduce the intestinal absorption of co-administered drugs.

Hepatic/Biliary/Pancreatic

Lanreotide may reduce gall bladder motility and lead to gall stone formation. Gall bladder ultrasonography is therefore advised at the start of treatment and periodically thereafter.

In hepatic impairment, an increase in Volume of Distribution, Mean Residence Time, AUC, and half-life were observed. Clearance was reduced by 30% in moderate to severe hepatically impaired patients (see Action and Clinical Pharmacology, Pharmacokinetics, Special Populations and Conditions).

Acromegaly

It is recommended that patients with moderate or severe hepatic impairment receive a starting dose of lanreotide of 60 mg (see DOSAGE AND ADMINISTRATION).
Patients with moderate or severe hepatic impairment have not been studied for an extended dosing interval of Somatuline Autogel 120 mg every 6 or 8 weeks (see Detailed Pharmacology, Pharmacokinetics of Somatuline Autogel in Patients with Acromegaly).

Enteropancreatic NETs

Somatuline Autogel has not been studied in patients with mild, moderate, or severe hepatic impairment (as per Child-Pugh score).

Immune

Allergic reactions (including angioedema and anaphylaxis) has been reported following administration of Somatuline Autogel (See Adverse Reactions section.) Use of Somatuline Autogel is contraindicated in patients with a history of hypersensitivity to lanreotide.

Renal

Acromegaly

Subjects with severe renal impairment show an approximately 2-fold decrease in total serum clearance of lanreotide, with a consequent increase in half-life and AUC (see Action and Clinical Pharmacology, Pharmacokinetics, Special Populations and Conditions). It is recommended that patients with moderate or severe renal impairment receive a starting dose of lanreotide of 60 mg (see DOSAGE AND ADMINISTRATION).

Patients with moderate or severe renal impairment have not been studied for an extended dosing interval of Somatuline Autogel 120 mg every 6 or 8 weeks (see Detailed Pharmacology, Pharmacokinetics of Somatuline Autogel in Patients with Acromegaly).

Enteropancreatic NETs

No effect was observed in total clearance of lanreotide in patients with mild to moderate renal impairment receiving Somatuline Autogel 120 mg. Patients with severe renal impairment were not studied.

Special Populations

Pregnant Women: There is very limited experience of pregnancy in patients treated with lanreotide, either during clinical trials or from post marketing reports.

Studies in animals showed a transitory growth retardation of offspring prior to weaning. Although no teratogenic effects have been observed in animals, Somatuline Autogel should be administered to pregnant women only if clearly needed.

Nursing Women: It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk. Somatuline Autogel should not be administered to breast-feeding women.

Pediatrics (< 16 years of age): There is no experience of the use of the product in children and therefore the use of Somatuline Autogel in children cannot be advised.

Geriatrics (> 65 years of age): Elderly subjects show an increase in half-life and mean residence time compared to healthy young subjects (see Action and Clinical Pharmacology, Pharmacokinetics, Special Populations and Conditions). It is not necessary to alter the starting dose of Somatuline Autogel in elderly patients (see DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

Acromegaly

Evaluation of GH and IGF-1 levels are useful markers of the disease progression and effectiveness of treatment (see Dosage and Administration section).

Acromegaly and enteropancreatic NETs

In patients suffering from cardiac disorders prior to lanreotide initiation, sinus bradycardia may occur and therefore heart rate should be monitored.

The principal pharmacodynamic interaction that may occur is the inhibition of glucagon secretion which may lead to the onset of hypoglycemia in treated diabetic patients, notably insulin-dependent patients. Thus, the insulin requirements in insulin-dependent diabetic patients may be reduced. Therefore blood glucose levels should be monitored when lanreotide treatment is initiated or when the dosage is attuned. The treatment of diabetic patients should be adjusted accordingly.

Lanreotide may reduce gall bladder motility and lead to gall stone formation. Gall bladder ultrasonography is therefore advised at the start of treatment and periodically thereafter.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The adverse reactions commonly reported with lanreotide administration are predominantly local (at injection site) and gastrointestinal.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Data for the treatment of acromegaly are provided from the pivotal clinical trial using Somatuline Autogel (Study 717) in 108 patients with acromegaly.

Data for the treatment of enteropancreatic Neuroendocrine Tumors are collected from the pivotal clinical trial using Somatuline Autogel (Study 726) conducted in 204 patients with enteropancreatic NETs.

Acromegaly Study 717

Study 717 was a randomized, double-blind placebo-controlled study, conducted in 108 acromegalic patients treated for one year. Patients received a total of 13 injections at 28 day intervals (one injection of placebo plus 12 injections of Somatuline Autogel or 13 injections of Somatuline Autogel). The dose could be adapted every 4 injections based on GH and IGF-1 levels.

The total exposure to Somatuline Autogel over the three phases of the study is summarised below.

Table 1. Total exposure to Somatuline Autogel during all three phases in Study 717 (Safety Population)

Statistic	Cumulative lanreotide dose (mg)	Average monthly lanreotide dose (mg)[1]	Duration of active treatment (days)[2]
N	107	107	107
Median	1140.0	98.6	364.0
Mean ± SD	1196.4 ± 301.6	96.4± 20.4	348.0 ± 48.7
Minimum, Maximum	270, 1560	58.8, 121.3	86, 400

[1] [Cumulative lanreotide dose/duration of active treatment] × 28.
[2] [Date of last lanreotide dose – date of first lanreotide dose] + 28.

Most Commonly Reported TEAEs

The incidence of treatment emergent adverse events for Somatuline Autogel 60 mg, 90 mg 120 mg compared to placebo as investigated during the first phase of Study 717 are provided in Table 2.

Table 2. Most commonly (≥5%) reported TEAEs during the double-blind phase (1 month = 1 injection) in Study 717 (Safety Population) by dose

Preferred Term	Somatuline Autogel: 60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)	Overall (N = 83)	Placebo (N = 25)	Total (N = 108)*
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Any adverse event	*11 (41)*	*19 (70)*	*20 (69)*	*50 (60)*	*9 (36)*	*59 (55)*
Diarrhoea	3 (11)	10 (37)	13 (45)	26 (31)	0	26 (24)
Abdominal pain	2 (7)	2 (7)	2 (7)	6 (7)	1 (4)	7 (6)
Bradycardia	3 (11)	2 (7)	2 (7)	7 (8)	0	7 (6)
Weight decrease	2 (7)	4 (15)	1 (3)	7 (8)	0	7 (6)
Anaemia	1 (4)	4 (15)	1 (3)	6 (7)	0	6 (6)
Flatulence	0	2 (7)	3 (10)	5 (6)	0	5 (5)

* Total number of patients included in the safety population for this study phase is 108.

The incidence of the most commonly reported related AEs, i.e., those reported in ≥2% of patients for the Somatuline Autogel Study 717 are presented in Table 3 by dose of onset. The majority of AEs observed in this study were mild to moderate in intensity. This table includes all TEAEs which began after the injection of Somatuline Autogel, therefore it excludes TEAEs which occurred in patients receiving placebo in the initial double blind phase. The number of patients included in each dose group is based on the total number of patients who received at least one dose at that dose level; also provided is the total across the three dose groups.

The injections were well tolerated. Injection site reactions, primarily reports of injection site mass and injection site pain, were infrequently reported over the 52-week study occurring in 9% and 9% of patients, respectively.

Table 3. Treatment Emergent Adverse Events Related to Somatuline Autogel Reported in ≥ 2% of Total Patients on Somatuline Autogel in Study 717 (Safety Population) by Dose of Onset

Adverse Event by Body System	Somatuline Autogel: 60 mg (N = 46)	90 mg (N = 66)	120 mg (N = 74)	Total (N = 107*)
	N (%)	N (%)	N (%)	N (%)
Any AE	23 (50)	33 (50)	51 (69)	72 (67)
Application Site Disorders				
Injection site mass	2 (4)	2 (3)	7 (9)	10 (9)
Injection site pain	3 (7)	3 (5)	4 (5)	10 (9)
Injection site reaction	0 (0)	1 (2)	2 (3)	3 (3)
Injection site bleeding	0 (0)	1 (2)	1 (1)	2 (2)
General Disorders				
Fatigue	1 (2)	4 (6)	3 (4)	8 (7)
Back pain	2 (4)	0 (0)	1 (1)	3 (3)
Malaise	0 (0)	0 (0)	2 (3)	2 (2)
Chest pain	0 (0)	0 (0)	2 (3)	2 (2)
Cardiovascular disorders				
Hypertension aggravated	2 (4)	2 (3)	1 (1)	5 (5)
Heart murmur	0 (0)	0 (0)	2 (3)	2 (2)

Adverse Event by Body System	Somatuline Autogel:			
	60 mg (N = 46)	90 mg (N = 66)	120 mg (N = 74)	Total (N = 107*)
	N (%)	N (%)	N (%)	N (%)
Central & Peripheral nervous system disorders				
Dizziness	2 (4)	0 (0)	2 (3)	4 (4)
Headache	2 (4)	0 (0)	2 (3)	4 (4)
Vertigo	0 (0)	2 (3)	0 (0)	2 (2)
GI system disorders				
Diarrhoea	10 (22)	19 (29)	34 (46)	50 (47)
Abdominal pain	5 (11)	8 (12)	10 (14)	21 (20)
Flatulence	2 (4)	3 (5)	7 (9)	11 (10)
Nausea	3 (7)	2 (3)	5 (7)	10 (9)
Vomiting	1 (2)	0 (0)	3 (4)	4 (4)
Constipation	1 (2)	1 (2)	2 (3)	4 (4)
Dyspepsia	1 (2)	4 (6)	1 (1)	6 (6)
Anorexia	0 (0)	1 (2)	2 (3)	3 (3)
Heart rate and rhythm disorders				
Bradycardia	7 (15)	5 (8)	3 (4)	14 (13)
Liver and biliary system disorders				
Cholelithiasis and/or gallbladder sludge	8 (17)	8 (12)	18 (24)	32 (30)
Gall bladder disorder	3 (7)	3 (5)	2 (3)	8 (7)
Bilirubinaemia	1 (2)	1 (2)	0 (0)	2 (2)
Hepatomegaly	0 (0)	1 (2)	1 (1)	2 (2)
Metabolic and nutritional disorders				
Hyperglycaemia Weight	3 (7)	2 (3)	3 (4)	8 (7)
decrease Hypoglycaemia	3 (7)	3 (5)	3 (4)	9 (8)
Hypercholesterolaemia	1 (2)	1 (2)	0 (0)	2 (2)
Phosphatase alkaline increased	2 (4)	1 (2)	0 (0)	2 (2)
	0 (0)	1 (2)	1 (1)	2 (2)
Musculo-skeletal system disorders				
Arthralgia	1 (2)	5 (8)	1 (1)	6 (6)
Myalgia	1 (2)	1 (2)	1 (1)	3 (3)
Muscle weakness	1 (2)	0 (0)	1 (1)	2 (2)
Skeletal pain	0 (0)	1 (2)	1 (1)	2 (2)
Myo Endo Pericardial & Valve disorders				
Heart valve disorders	0 (0)	1 (2)	2 (3)	3 (3)
Aortic stenosis	1 (2)	0 (0)	1 (1)	2 (2)
Aortic valve incompetence	1 (2)	2 (3)	0 (0)	2 (2)
Myocardial infarction	0 (0)	0 (0)	2 (3)	2 (2)
Psychiatric disorders				
Depression	1 (2)	1 (2)	0 (0)	2 (2)
Nervousness	1 (2)	0 (0)	1 (1)	2 (2)
Red blood cell disorders				
Anaemia	2 (4)	2 (3)	2 (3)	6 (6)
Respiratory system disorders				
Dyspnoea	1 (2)	0 (0)	2 (3)	3 (3)
Skin and Appendages disorders				
Alopecia	5 (11)	3 (5)	5 (7)	11 (10)
Hair disorder nos	1 (2)	0 (0)	2 (3)	3 (3)
Nail disorder	2 (4)	1 (2)	0 (0)	3 (3)

Adverse Event by Body System	Somatuline Autogel:			
	60 mg (N = 46)	90 mg (N = 66)	120 mg (N = 74)	Total (N = 107*)
	N (%)	N (%)	N (%)	N (%)
White cell and res disorder Leucopenia	0 (0)	0 (0)	2 (3)	2 (2)

* Total number of patients included in the safety population for these study phases is 107.

Note that arthralgia, bradycardia, and constipation are symptoms commonly reported among patients with acromegaly; in addition, these patients also experience hyperglycaemia related to their underlying condition.

Other related adverse events occurring at an incidence between <2% and ≥ 1% reported in the pivotal clinical study 717:

Application Site Disorders: injection site inflammation

General Disorders: asthenia, oedema, pain, sweating increased

Cardiovascular Disorders: cardiomegaly, ECG abnormal

Central and Peripheral Nervous System Disorders: dysaesthesia, gait abnormal, hypoaesthesia, paraesthesia

Endocrine Disorders: hypothyroidism

Gastro-Intestinal System Disorders: change in bowel habits, gastro-intestinal disorder nos, gastroesophageal reflux, haemorrhoids, pancreatitis

Hearing and Vestibular Disorders: tinnitus

Heart Rate and Rhythm Disorders: arrhythmia atrial, arrhythmia ventricular, bundle branch block, heart block

Liver and Biliary System Disorders: cholecystitis, hepatic neoplasm, hepatocellular damage, hepatosplenomegaly

Metabolic and Nutritional Disorders: diabetes mellitus, diabetes mellitus aggravated, vitamin B12 deficiency

Musculo-Skeletal System Disorders: bursitis

Myo Endo Pericardial & Valve Disorders: atrial septal defect, mitral insufficiency

Neoplasm: hepatic neoplasm, neoplasm nos

Psychiatric Disorders: anxiety, appetite increased, impotence, insomnia

Reproductive Disorders: endometrial disorder

Respiratory System Disorders: bronchitis, rhinitis

Secondary Terms: cyst nos

Urinary System Disorders: dysuria, renal pain

Vascular (Extracardiac) Disorders: peripheral ischemia

Vision Disorders: cataract, corneal deposits

Enteropancreatic NETs Study 726

Study 726 was a randomized, double-blind placebo-controlled study, conducted in 204 enteropancreatic NETs patients treated for 96 weeks. Somatuline Autogel 120 mg fixed dose was administered every 4 weeks.

Safety results are based on a median follow-up of approximately 96 weeks in the group treated with Somatuline Autogel 120 mg and 60 weeks in the group treated with placebo. The rates of discontinuation due to treatment emergent adverse reactions were 3% in the Somatuline Autogel arm and 2.9% in the placebo arm.

Table 4 compares the treatment-emergent adverse reactions reported with an incidence of ≥5% in patients receiving Somatuline Autogel 120 mg administered every 4 weeks versus placebo. The majority of these events were mild to moderate in severity.

Table 4: Adverse Reactions Occurring in ≥ 5% of Somatuline Autogel-Treated Patients with enteropancreatic NETs in Study 726

Body System Preferred Term	**Somatuline Autogel 120 mg, (N=101) n (%)**	**Placebo (N=103) n (%)**
Any TEAE	**89 (88)**	**93 (90)**
Gastrointestinal Disorders	**68 (67)**	**65 (63)**
Diarrhoea	35 (35)	36 (35)
Abdominal pain	24 (24)	17 (17)
Vomiting	19 (19)	9 (9)
Nausea	14 (14)	14 (14)
Constipation	12 (12)	13 (13)
Flatulence	12 (12)	9 (9)
Abdominal pain upper	8 (8)	8 (8)
Abdominal discomfort	5 (5)	3 (3)
Infections and infestations	**41 (41)**	**46 (45)**
Nasopharyngitis	9 (9)	16 (16)
Urinary tract infection	9 (9)	9 (9)
General Disorders and Administration Site Disorders	**36 (36)**	**43 (42)**
Fatigue	10 (10)	15 (15)
Asthenia	8 (8)	5 (5)
Injection site pain	8 (8)	4 (4)
Oedema peripheral	5 (5)	7 (7)
Musculoskeletal and Connective Tissue Disorders	**34 (34)**	**24 (23)**
Back pain	12 (12)	11 (11)
Arthralgia	10 (10)	9 (9)
Musculoskeletal pain	7 (7)	3 (3)
Muscle spasms	5 (5)	4 (4)
Nervous System Disorders	**32 (32)**	**19 (18)**
Headache	16 (16)	11 (11)
Dizziness	9 (9)	2 (2)
Lethargy	5 (5)	4 (4)

Metabolism and Nutrition Disorders	32 (32)	19 (18)
Decreased appetite	10 (10)	9 (9)
Diabetes mellitus	7 (7)	4 (4)
Hyperglycemia	6 (6)	0
Dehydration	5 (5)	1 (1)
Vascular Disorders	**24 (24)**	**18 (18)**
Hypertension	13 (13)	5 (5)
Skin and subcutaneous tissue disorders	**22 (22)**	**21 (20)**
Pruritus	5 (5)	5 (5)
Alopecia	5 (5)	4 (4)
Rash	5 (5)	3 (3)
Hepatobiliary Disorders	**20 (20)**	**10 (10)**
Cholelithiasis	14 (14)	7 (7)
Investigations	**18 (18)**	**14 (14)**
Weight decreased	8 (8)	9 (9)
Pancreatic enzymes decreased	6 (6)	0
Respiratory, Thoracic, and Mediastinal Disorders	**17 (17)**	**15 (15)**
Dyspnea	6 (6)	1 (1)
Cough	5 (5)	3 (3)
Oropharyngeal pain	5 (5)	3 (3)
Blood and Lymphatic System Disorders	**8 (8)**	**7 (7)**
Anemia	6 (6)	1 (1)

TEAE = Treatment-emergent adverse event
Dictionary Name = MedDRA 16.0
A patient is counted only once for each body system and preferred term.

Other related adverse events occurring at an incidence between <5% and ≥1% in the clinical study 726:

Gastrointestinal disorders: pancreatic insufficiency, abdominal distension, steatorrhoea, abdominal pain lower, abdominal rigidity, abnormal feces, defecation urgency, dyspepsia, feces pale/discoloured

General disorders and administrative site conditions: injection site reactions (induration, granuloma, mass, nodule, pruritus, swelling, rash), pyrexia, chills, influenza like illness ***Hepatobiliary disorders***: biliary fistula, hepatic failure

Nervous system disorders: syncope

Investigations: blood glucose decreased, gamma-glutamyltransferase increased

Metabolism and nutrition disorders: glucose tolerance impaired

Psychiatric disorders: nervousness, depression

Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus generalized, skin lesion, dry skin

Musculoskeletal and connective tissue disorders: myalgia

Cardiac disorders: bradycardia

Eye disorders: vision blurred

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Acromegaly Study 717
Skin and appendages disorders: allergic skin reaction
Gastrointestinal disorders: steatorrhea
Administration site disorders: injection site nodule

Enteropancreatic NETs Study 726
Skin and appendages disorders: allergic skin reaction

Abnormal Hematologic and Clinical Chemistry Findings

Acromegaly Study 717
Slight anaemia is not uncommon in acromegaly patients. In the pivotal Somatuline Autogel study no clinically meaningful changes in haematology or chemistry parameters were noted. Only small mean decreases from baseline to week 52 and LVA were noted for all red cell parameters, including haemoglobin, hematocrit and red blood cell count. No trends were noted for changes from baseline in red cell or clinical chemistry parameters.

In two additional studies with Somatuline Autogel there were no clinically significant changes in any haematology or biochemistry parameters over the course of treatment.

Enteropancreatic NETs Study 726
No clinically meaningful shifts in any of the hematology parameters were observed. Approximately 23% of patients in the Somatuline Autogel arm experienced a shift in their HbA1c (%) from normal at baseline to high at the last value compared to 4% of patients in the placebo arm.

Post-Market Adverse Drug Reactions
Rarely post- injection episodes of malaise with signs of dysautonomia were reported. Rare cases of persisting induration at injection site were reported.

Allergic reactions associated with lanreotide (including angioedema, anaphylaxis, and hypersensitivity) have been reported in the postmarketing environment.

DRUG INTERACTIONS

Serious Drug Interactions

Concomitant administration of lanreotide injection with cyclosporin may decrease blood levels of cyclosporin (see Drug-Drug Interactions section)

Overview
The gastrointestinal effects of Somatuline Autogel may reduce the intestinal absorption of co-administered drugs. No significant interaction was found with vitamin K when administered concomitantly with lanreotide.

Interactions with highly plasma bound drugs are unlikely in view of the moderate binding of lanreotide to serum proteins (78% mean serum binding) (see Extrinsic Factor Pharmacokinetic Studies section).

Limited published data indicate that somatostatin analogues might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that lanreotide may have this effect, other medicinal products mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. terfenadine) should therefore be used with caution.

Drug-Drug Interactions
Concomitant administration of lanreotide injection with cyclosporin may decrease blood levels of cyclosporin, hence blood levels of cyclosporin should be monitored. Concomitant administration of lanreotide and bromocriptine increases the availability of bromocriptine.
The drugs listed in this section are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Acromegaly
Patients should begin treatment with Somatuline Autogel 90 mg given via deep subcutaneous route, at 4 week intervals for 3 months. After 3 months dosage may be adapted as follows:

- GH >1 to ≤ 2.5 ng/mL, IGF-1 normal and clinical symptoms controlled: Maintain Somatuline Autogel dosage at 90 mg every 4 weeks
- GH > 2.5 ng/mL, IGF-1 elevated and/or clinical symptoms uncontrolled: Increase Somatuline Autogel dosage to 120 mg every 4 weeks
- GH ≤1 ng/mL, IGF-1 normal and clinical symptoms controlled: Reduce Somatuline Autogel dosage to 60 mg every 4 weeks.

Thereafter, the dose should be adjusted according to the response of the patient as judged by a reduction in symptoms and/or in GH and /or IGF-1 levels.

The starting dose in patients with moderate or severe hepatic or renal impairment should be 60 mg Somatuline Autogel via the deep subcutaneous route, at 4 week intervals for 3 months, followed by dose adjustment as described above (see Action and Clinical Pharmacology, Special Populations and Conditions).

It is not necessary to alter the starting dose in elderly patients (see Action and Clinical Pharmacology, Pharmacokinetics, Special Populations and Conditions).

Patients who are controlled on Somatuline Autogel 60 mg or 90 mg may be considered for an extended dosing interval of Somatuline Autogel 120 mg every 6 or 8 weeks. GH and IGF-1 levels should be obtained 6 weeks after this change in dosing regimen to evaluate the persistence of patients' response.

Continued monitoring of patients' response with dose adjustments for biochemical and clinical symptom control is recommended.

Patients with moderate or severe hepatic or renal impairment have not been studied for an extended dosing interval of Somatuline Autogel 120 mg every 6 or 8 weeks (see Detailed Pharmacology, Pharmacokinetics of Somatuline Autogel in Patients with Acromegaly).

Enteropancreatic NETs
The recommended dose of Somatuline Autogel is 120 mg administered every 4 weeks by deep subcutaneous injection in the superior external quadrant of the buttock. Treatment with Somatuline Autogel should be discontinued upon disease progression.

Missed Dose
If a dose is missed, the next dose should be administered as soon as possible.

Administration
The injection may be given by a healthcare professional or, for patients considered by their healthcare professional to be on a stable dose of Somatuline Autogel, by another appropriately trained individual. Alternatively, such patients may self-administer the product after appropriate training. The decision regarding administration by the patient or a trained individual should be taken by the healthcare professional.

Somatuline Autogel should be injected via the deep subcutaneous route in the superior external quadrant of the buttock. In the case of self-administration, the injection should be given in the upper outer thigh.

Regardless of the site of administration, the skin should be stretched prior to injection. The needle should be inserted rapidly to its full length, perpendicularly to the skin. **The injection site should be alternated between the right and left sides.**

Somatuline Autogel is provided in a ready-to-use, sterile, pre-filled syringe fitted with an automatic safety system that automatically locks in place following administration of the product, to help prevent needle stick injury after use. Somatuline Autogel is for immediate and single use following first opening. No reconstitution is required.

OVERDOSAGE

If overdose occurs, symptomatic management is indicated. Experience with lanreotide overdose in humans consists of a single case, a 52-year-old acromegalic patient with medical history of diabetes mellitus and hypertension, who had received as a result of drug misuse a 30mg lanreotide injection daily for 2 months. No acute symptoms or pharmacological signs of overdose were reported. One week after the last injection he experienced a myocardial infarction.

For management of a suspected drug overdose please contact your local Poison Control Centre

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Lanreotide is a synthetic octapeptide analogue of natural somatostatin. Somatostatin is an endogenous peptide present in several areas of the central nervous system and in the gastrointestinal tract. It has very powerful inhibitory effects on different cell types.

Like natural somatostatin, lanreotide is a peptide inhibitor of numerous endocrine, neuroendocrine and exocrine mechanisms. It exhibits high affinity for both the somatostatin Type 2 (SSTR2) and Type 5 (SSTR5) receptors that are found in both the pituitary gland and pancreas, as well as in growth hormone-secreting pituitary tumors. Conversely, it has a much lower affinity for somatostatin 1, 3 and 4 receptors. This confers relative specificity of action on growth hormone secretion, making it suitable for the treatment of acromegaly.

Table 5: Inhibition of Radioligand Binding to Human Recombinant Somatostatin Receptors (Ki) Comparing lanreotide and Octeotride (Study RO-10)

Receptor	Lanreotide (nM) Mean±SEM	Octreotide (nM) Mean±SEM
hSSTR1	2022 ± 394	1154 ± 307
hSSTR2	0.75 ± 0.09	0.53 ± 0.07
hSSTR3	75.2± 2.7	40.2 ± 8.1
hSSTR4	1826 ± 264	5029 ± 2001
hSSTR5	5.25 ± 0.80	6.77 ± 0.96

There are a number of mechanisms by which somatostatin analogues may inhibit cell proliferation. A direct antitumor effect may result from the activation of somatostatin receptors on tumor cells leading to modulation of intracellular signaling pathways. Somatostatin analogues may also produce an indirect antitumor effect through the inhibition of mitogenic growth factors such as insulin-like growth factor and inhibition of tumor angiogenesis through interaction with somatostatin receptors on endothelial cells and monocytes.

Pharmacodynamics

Primary pharmacology studies using lanreotide showed that lanreotide dose-dependently reduced spontaneous GH secretion in healthy volunteers and acromegalic patients.

Population PK/PD relationship between GH inhibition and lanreotide serum concentration was reported in two analyses including 129 and 107 patients respectively treated with Somatuline Autogel. Results from these studies indicated that lanreotide has a maximum capacity of GH inhibition of 82%. Lanreotide concentration providing half of the maximum inhibition of GH (EC50) in responder patients was 0.206 to 0.612 ng/mL and the median lanreotide serum level needed to decrease the GH to 2.5 ng/mL (C2.5) was 0.95 to 1.1 ng/mL. Non-responders do not respond to lanreotide treatment even with high lanreotide concentrations.

An exploratory study in previously untreated patients with large pituitary adenomas suggests that Somatuline Autogel induces pituitary tumour volume reduction.

The potential for formation of lanreotide antibodies has been examined during the conduct of efficacy studies using lanreotide. Laboratory investigations showed that non-specific binding (NSB) >10% was present in a small minority of patients treated with lanreotide, and in a few patients the binding was specific for lanreotide and associated with serum antibodies.

Somatostatin was not bound by any of the specimens tested. The safety profiles of patients with NSB values < 10%, between 10 and 30% and > 30% were similar and there was no evidence that any of the serious adverse events that were reported were due to hypersensitivity reactions. Clinical investigations failed to demonstrate any differences in response to lanreotide treatment between patients with NSB >10% or NSB >25% versus patients who did not exhibit NSB at these levels.

In the enteropancreatic NETs pivotal trial, the majority of patients with elevated levels of plasma chromogranin A and/or urinary 5-HIAA (5-hydroxyindoleacetic acid) who received treatment with Somatuline Autogel had a decrease in the levels of these tumour markers.

Pharmacokinetics

Pharmacokinetics of Somatuline Autogel in Healthy Volunteers

Table 6a: Summary of Lanreotide's Pharmacokinetic Parameters in Healthy Volunteers After a Single Dose of Somatuline Autogel 60, 90 and 120mg

Parameter	60 mg		90 mg		120 mg	
	Mean	SD	Mean	SD	Mean	SD
C_{max} (ng/mL)	4.246	1.934	8.391	4.915	6.785	3.641
AUC_{∞} (ng/mL/h)	1904.98	564.09	2984.35	1214.04	3552.26	947.33
t_{max} (h)*	8 (4 to 336)	--	12 (4 to 336)	--	7 (2 to 48)	--
$t_{1/2}$ (h)	664	455	860	431	816	334
t_{lag} (h)	<1.0	0.0	<1.0	0.0	<1.0	0.0
F (%)	83.25	34.56	78.14	25.87	80.87	24.18

* = Median (range) value

Pharmacokinetics of Somatuline Autogel in Patients with Acromegaly

Table 6b: Summary of Lanreotide's Pharmacokinetic Parameters in Acromegalic Patients After Four Doses of Somatuline Autogel 60, 90 and 120mg

Parameter	60 mg		90 mg		120 mg	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
$C_{max,ss}$ (ng/mL)	3.821	0.509	5.694	1.672	7.685	2.470
AUC_{τ} (ng·h/mL)	1650.96	204.72	2042.64	410.40	3039.84	663.84
$T_{max,ss}$ (d)*	84.62	(84.17–85.99)	84.29	(84.17–85.99)	84.66	(84.33–85.97)
$C_{min,ss}$ (ng/mL)	1.822	0.304	2.511	0.882	3.762	1.012
C_{avg} (ng/mL)	2.457	0.305	3.040	0.611	4.523	0.988
PTF (%)	81	--	108	--	86	--

*Median (range) value
PTF = Peak Trough Fluctuation

Distribution: Studies with lanreotide after intravenous administration at doses of 7, 21 and 42 µg/kg have demonstrated that it shows limited extravascular distribution, with a mean V_{ss} of 0.186 to 0.194 L/kg.

Lanreotide human serum proteins binding studies were performed *in vitro* obtaining a range of values from 79 to 83 % at lanreotide concentrations between 12 and 60 ng/ml.

Metabolism: Lanreotide is metabolised extensively in the gastrointestinal tract after biliary excretion.

The values of apparent elimination half-life of Somatuline Autogel after deep s.c. administration range from 28 to 36 days.

Excretion: After a single s.c. dose of 3 mg of lanreotide, less than 1% of the administered dose was recovered in urine and renal clearance was < 1% of total plasma clearance. After s.c. infusion of lanreotide, the fraction of lanreotide excreted in the urine at steady state was 1% to 5% for a dose of 0.75 mg/day.

Data for fecal excretion showed that less than 0.5% of the administered dose was recovered over a 24 hour period at steady state. Therefore, urinary and faecal excretion of unchanged lanreotide represents only a small fraction of the total dose administered.

No gender differences were found in PK parameters.

Pharmacokinetics of Somatuline Autogel in Patients with enteropancreatic NETs

In a population PK analysis in 290 NETs patients receiving Somatuline Autogel, rapid initial

release of lanreotide was seen with mean C_{max} values of 7.49 ± 7.58 ng/mL reached within the first day after a single injection. Steady-state concentrations were reached after 4 to 5 injections of Somatuline Autogel 120 mg every 4 weeks and were sustained up to the last assessment (up to 96 weeks after the first injection). At steady state, the mean C_{max} values were 13.9 ± 7.44 ng/mL and the mean trough serum levels were 6.56 ± 1.99 ng/mL. The mean apparent terminal half-life was 49.8 ± 28.0 days.

Special Populations and Conditions

Pediatrics: No studies in pediatrics were performed in this indication.

Geriatrics: with the immediate-release formulation, healthy elderly subjects showed an 85% increase in half-life and a 65% increase in mean residence time of lanreotide compared to healthy young volunteers. However, there was no change in either AUC or C_{max} of lanreotide in elderly subjects compared to healthy young subjects (see Detailed Pharmacology, Pharmacokinetics of Somatuline Autogel in Healthy Volunteers). It is not necessary to alter the starting dose in elderly patients.

In a population PK analysis of NETs patients treated with Somatuline Autogel, including 122 patients aged 65 to 85 years, no effect of age on clearance and volume of distribution of lanreotide was observed.

Hepatic Insufficiency: In patients with hepatic impairment, an increase in volume of distribution, mean residence time, AUC, and half-life were observed with the lanreotide immediate-release formulation. Clearance was reduced by 30% in patients with moderate to severe hepatic impairment, suggesting that clearance of lanreotide does not only depend on hepatic function (see Detailed Pharmacology, Intrinsic Factor Pharmacokinetic Studies). Patients with moderate to severe hepatic impairment should begin treatment with Somatuline Autogel 60 mg.

Patients with moderate or severe hepatic impairment have not been studied for an extended dosing interval of Somatuline Autogel 120 mg every 6 or 8 week (see Detailed Pharmacology, Pharmacokinetics of Somatuline Autogel in Patients with Acromegaly). No NETs patients with hepatic impairment (as per Child-Pugh score) were studied.

Renal Insufficiency: Lanreotide immediate-release formulation has been studied in patients with end-stage renal function on dialysis, but has not been studied in patients with mild or moderaterenal impairment. In subjects with severe renal impairment, total serum clearance of lanreotide is decreased by approximately two-fold, with a consequent two-fold increase in half-life and AUC (see Detailed Pharmacology, Intrinsic Factor Pharmacokinetic Studies). Patients with moderate to severe renal impairment should begin treatment with Somatuline Autogel 60 mg.

Patients with moderate or severe renal impairment have not been studied for an extended dosing interval of Somatuline Autogel 120 mg every 6 or 8 weeks (see Detailed Pharmacology, Pharmacokinetics of Somatuline Autogel in Patients with Acromegaly).

No effect on clearance of lanreotide was observed in a population PK analysis of NETs patients, including 165 patients with mild or moderate renal impairment (106 and 59, respectively) treated with Somatuline Autogel. NETs patients with severe renal impairment were not studied.

STORAGE AND STABILITY

Store under refrigeration (+2°C to +8°C) in its original package.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Somatuline Autogel is supplied in a polypropylene, sterile, pre-filled syringe with an automatic needle protection system and fitted with a stainless steel needle.

Each pre-filled syringe is packed in a polyethylene terephtalate/aluminium/polyethylene laminated pouch.

Box of one individual 60mg dose in a 0.5 ml syringe with a needle (1.2 mm x 20 mm).
Box of one individual 90mg dose in a 0.5 ml syringe with a needle (1.2 mm x 20 mm).
Box of one individual 120mg dose in a 0.5 ml syringe with a needle (1.2 mm x 20 mm).

Somatuline Autogel is an extended release preparation intended for deep subcutaneous injection.

The only excipients are water for injection and glacial acetic acid (for pH adjustment).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

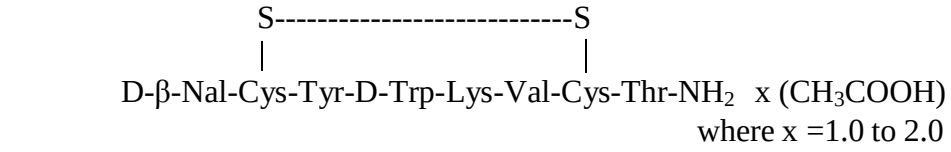
Common name: Lanreotide acetate (USAN)

Chemical name: [cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate

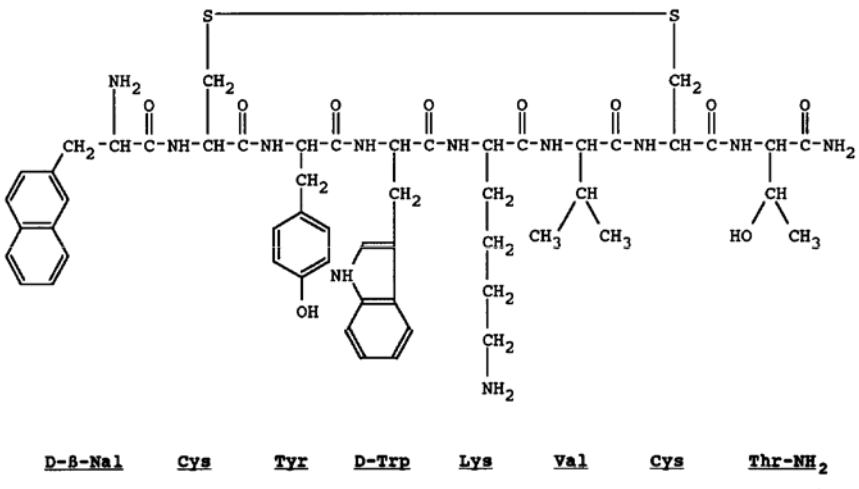
Molecular formula: $C_{54}H_{69}N_{11}O_{10}S_2$ $(CH_3COOH)x$
where x =1.0 to 2.0

Molecular mass: 1096.34 g/mol (base)

Structural formula:



or



x (CH_3COOH)
where x =1.0 to 2.0

Physicochemical properties:

Appearance: White to off-white amorphous powder.

Solubility: The solubility of lanreotide in aqueous solution varies little with pH, except at extreme pH values, most notably at alkaline pH.

CLINICAL TRIALS

Acromegaly Study 717

The clinical efficacy of Somatuline Autogel was assessed in one pivotal clinical trial (E-28-52030-717). The study was a randomized, double blind, placebo-controlled study, conducted in 108 acromegalic patients treated for one year. Half (50%) of the patients had never been treated with a somatostatin analog or dopamine agonist, or had stopped treatment for acromegaly three or more months prior to their participation in the study. For inclusion into study 717, these patients were required to have a mean GH level > 5 ng/mL at their first visit. The other 50% of the patients had received treatment with a somatostatin analog or a dopamine agonist prior to study entry (requiring an appropriate wash-out of this therapy before receiving the first injection of Somatuline Autogel).

The median age of patients enrolled was 54.0 years with a range of 19-84 years. A similar number of males (n=51) and females (n=57) were treated and the median duration from diagnosis of acromegaly was approximately 3 years.

Upon entry, patients were randomly allocated to receive a deep s.c. injection of Somatuline Autogel 60mg, 90mg or 120 mg or placebo (3:1). After the initial placebo controlled phase, patients entered a fixed-dose phase where they received injections of Somatuline Autogel at 4 week intervals for 4 injections, followed by a dose-titration phase of 8 injections (a total of 13 injections; including placebo phase). During the titration phase the dose could be adapted after 3 months according to the patients' individual GH and IGF-1 levels.

Study results

Table 7. Results of study 717 in specific indication

Primary Endpoints	**Associated value and statistical significance (comparison Somatuline Autogel versus placebo)** **n/N - % - p value**
The proportion of patients with a >50% decrease in mean GH from baseline 4 weeks after a single injection, comparing each Autogel group (60, 90 and 120 mg) versus placebo. The combined Somatuline Autogel group was also compared to placebo.	Placebo: 0/25 - 0% Autogel 60 mg: 14/27 - 52% - $p < 0.001$ Autogel 90 mg: 12/27 - 44%; $p < 0.001$ Autogel 120 mg:26/29 - 90%; $p < 0.001$ Autogel Combined: 52/83 - 63%; $p < 0.001$
Secondary Endpoints	**Somatuline Autogel (all combined doses)** **n/N - %**
The proportion of patients with a >50% decrease in mean GH from baseline at weeks 16, 32, 52 and Last Value Available post-baseline (LVA).	Wk 16: 77/105 - 73% Wk 32: 82/103 - 80% Wk 52: 80/98 - 82% LVA: 82/107 - 77%
The proportion of patients with mean GH ≤ 2.5 ng/mL over time	Wk 16: 52/105 - 50% Wk 32: 59/103 - 57% Wk 52: 53/98 - 54% LVA: 55/107- 51%
The proportion of patients with normalized IGF-I over time	Wk 16: 58/105 - 55% Wk 32: 57/103 - 55% Wk 52: 58/98 - 59% LVA: 61/107 - 57%
The proportion of patients with mean GH ≤ 2.5 ng/mL and normalized IGF-I over time	Wk 16: 41/105 - 39% Wk 32: 46/103 - 45% Wk 52: 42/98 - 43% LVA: 43/106 - 41%
Symptoms	**Somatuline Autogel (all combined doses)**
	By the end of the study, the acromegaly symptoms of headache, perspiration, fatigue, swelling of extremities, and joint pain had improved from baseline or were stable in 88% to 94% of patients.

Enteropancreatic NETs Study 726

A Phase 3, 96-week, fixed-duration, randomized, double-blind, multicenter, placebo-controlled trial of Somatuline Autogel was conducted in patients with enteropancreatic neuroendocrine tumors to assess the antiproliferative effect of lanreotide.

Patients had non-functioning metastatic and/or locally advanced inoperable disease with histologically confirmed Grade 1 or a subset of Grade 2 (equivalent to Ki67 < 10%) tumors, originating in the pancreas, midgut, hindgut, or of unknown primary location.

Randomization was stratified by previous therapy at entry and the presence/absence of progression at baseline as assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.0) during a 3- to 6-month screening phase. Approximately 96% of patients had stable disease at baseline.

The primary endpoint was progression-free survival (PFS) measured as time to either disease progression by RECIST 1.0 or death within 96 weeks after first treatment administration., as assessed by a central, independent, radiological review.

Patients were randomized 1:1 to receive either Somatuline Autogel 120 mg every 4 weeks (n=101) or placebo (n=103). Baseline patient and disease characteristics are summarized in Table 8.

Table 8: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Trial of Patients with enteropancreatic-NETs

	Somatuline Autogel 120 mg (N=101)	**Placebo (N=103)**
Age (years)		
Mean (range)	63.3 (30 to 83)	62.2 (31 to 92)
Sex, n (%)		
Male	53 (52.5)	54 (52.4)
Female	48 (47.5)	49 (47.6)
Race, n (%)		
Asian	2 (2.0)	5 (4.9)
Black/African American	2 (2.0)	2 (1.9)
Caucasian/White	97 (96.0)	96 (93.2)
Primary tumor location, n (%)		
Pancreas	42 (41.6)	49 (47.6)
Midgut	33 (32.7)	40 (38.8)
Hindgut	11 (10.9)	3 (2.9)
Other/Unknown	15 (14.9)	11 (10.7)
Proliferation Index Ki67%, n (%)		
≤2%	52 (51.5)	51 (49.5)
>2% to <10%	31 (30.7)	29 (28.1)
Unknown[c]	18 (17.8)	23 (22.3)
Grade of tumor[d], n (%)		
G1	69 (68.3)	72 (69.9)
G2	32 (31.7)	29 (28.2)

	Somatuline Autogel 120 mg (N=101)	Placebo (N=103)
Missing	0	2 (1.9)
Hepatic tumor load, n (%)		
0% to ≤10%	49 (48.5)	58 (56.3)
>10% to ≤25%	13 (12.9)	17 (16.5)
>25% to <50%	39 (38.6)	28 (27.2)
Previous chemotherapy for NET , n (%)		
Yes	14 (13.9)	15 (14.6)
No	87 (86.1)	88 (85.4)
Previous surgery of the primary tumor, n (%)		
Yes	40 (39.6)	39 (37.9)
No	61 (60.4)	64 (62.1)
Baseline CgA, n (%)		
≤ULN	33 (32.7)	34 (33.0)
>1 to >2 ULN	66 (65.4)	66 (64.1)
Missing	2 (2.0)	3 (2.9)
Progression at baseline, n (%)		
Yes	4 (4.0)	5 (4.9)
No	97 (96.0)	98 (95.1)

N=total number of subjects in group; n=number of subjects with assessment
G1=Grade 1; G2=Grade 2; ULN=upper limit of normal; CgA=Chromogranin A
[c]The Ki67 is <10%, but the Ki67 could not be reliably quantified (these subjects were enrolled based on the mitotic index, which was ≤ 2 mitoses/10 HPF)
[d]G1=Mitotic count < 2 mitoses/10 HPF and/or Ki67 ≤ 2%; G2=Mitotic count 2-20 mitoses/10 HPF and/or Ki67 >2% to 20%

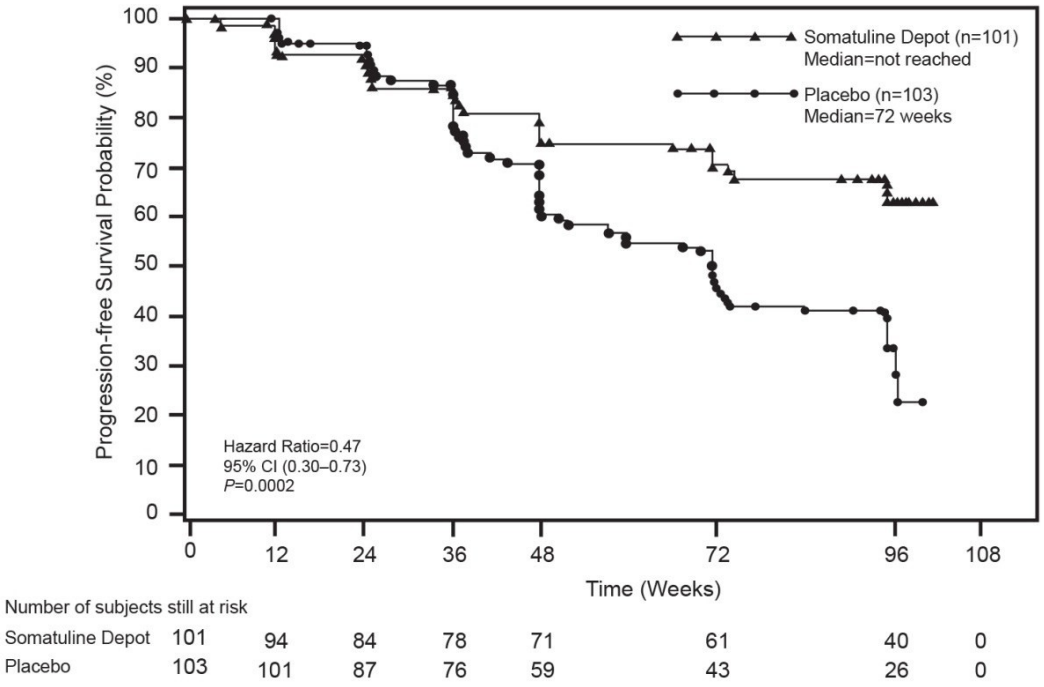
Monthly treatment with Somatuline Autogel demonstrated a statistically significant improvement in PFS, resulting in a 53% reduction in tumor progression or death when compared to placebo (p=0.0002). The median PFS for Somatuline Autogel was not reached at 96 weeks while the median PFS for placebo was 72 weeks, as shown in Table 9 and Figure 1.

Table 9: Efficacy Results of the Phase 3 Study

	Median Progression-free survival (weeks)		Hazard Ratio (95% CI)	Reduction in risk of progression or death	p-value
	Somatuline Autogel (n=101)	Placebo (n=103)			
All patients	> 96 weeks	72.0 weeks (95% CI: 48.6, 96.0)	0.47 (0.30, 0.73)	53%	0.0002
Primary tumour type					
Pancreas	**(n=42)**	**(n=49)**			
	> 96 weeks	48.6 weeks (95% CI: 37.7,73.1)	0.58 (0.32, 1.04)	42%	0.0637
Midgut	**(n=33)**	**(n=40)**			
	> 96 weeks	84.6 weeks (95% CI: 68.1, NC)	0.35 (0.16, 0.80)	65%	0.0091
Hindgut	**(n=11)**	**(n=3)**			
	> 96 weeks	97.7 weeks (95% CI: 48.1-97.7)	1.46 (0.16, 13.24)	-	0.7114
Unknown/other	**(n=15)**	**(n=11)**			
	> 96 weeks	60.0 weeks (95% CI: 25.1-NC)	0.20 (0.04, 1.03)	80 %	0.0341

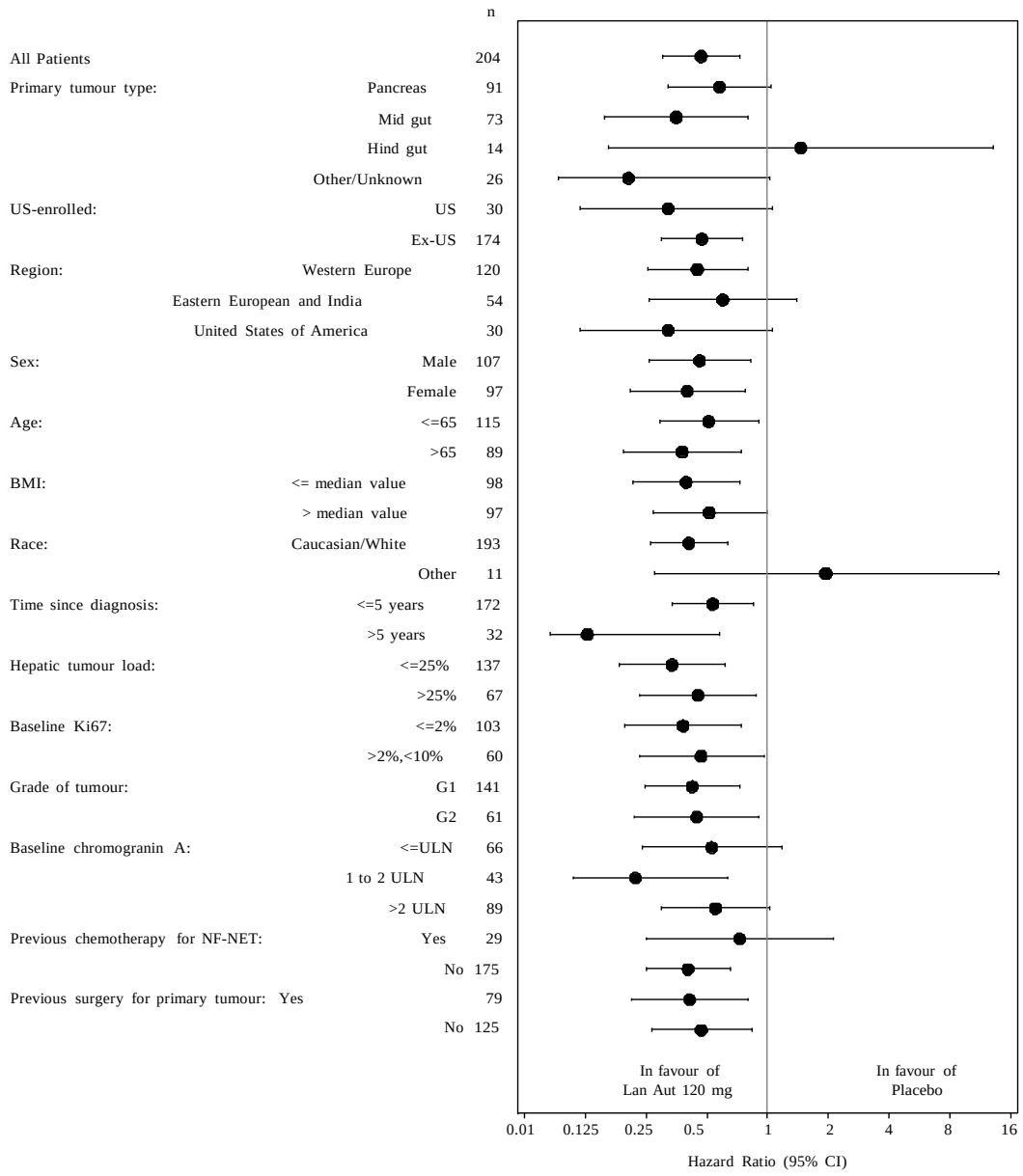
NC: not calculable

Figure 1: Kaplan-Meier Progression-Free Survival Curves



The beneficial effect of Somatuline Autogel in reducing the risk of progression or death was consistent, regardless of the location of primary tumor, hepatic tumor load, previous chemotherapy, baseline Ki67, tumor grade, age and of other pre-specified characteristics as shown in Figure 2.

Figure 2: Results of Subgroup analyses of PFS based on separate Cox Proportional Hazards models



Note: median value of BMI is 26.2 kg/m^2

DETAILED PHARMACOLOGY

Clinical pharmacodynamics

The dose and concentration of Somatuline Autogel was chosen with the help of results from an analysis of the relationship between lanreotide serum levels and GH plasma levels. This analysis was conducted using data from five clinical trials in which lanreotide was administered over a range of doses, routes and durations. The main finding from this analysis was that the

concentration of lanreotide required to decrease the GH levels to 2.5 ng/mL was between 2 ng/mL and 3.5 ng/mL (60% to 81% of patients showed GH normalisation at these concentrations). Non-responders do not respond to lanreotide treatment even with high lanreotide concentrations.

Secondary pharmacological effects

The secondary pharmacological effects of lanreotide are those observed with somatostatin analogs. Somatostatin is widely distributed in cells throughout the bodies of vertebrates and has pleiotropic actions. Therefore the effects of lanreotide on several physiological systems that are regulated by somatostatin such as inhibition of insulin, glucagons and somatostatin have been investigated.

Lanreotide provoked a physiological picture of slight glucose intolerance, characterized by decreased plasma levels of insulin and C-peptide and increased plasma levels of glucose. This effect was dose-related and attenuated over seven days of dosing. A study in patients with Type I or Type II diabetes mellitus evaluated the effects of a continuous, 21-day infusion of lanreotide. Lanreotide appeared to reduce the insulin requirements in patients with diabetes mellitus and had only a transient effect on blood glucose levels.

Five studies have been conducted to investigate the effects of lanreotide on digestive hormone secretions in healthy subjects. Similarly to somatostatin, lanreotide significantly reduced PP, motilin, and GIP levels (AUC values) and post prandial gastrin secretion, but did not affect secretin.

Somatostatin inhibits bile secretion and pancreatic secretion of bicarbonate and enzymes. Similarly lanreotide inhibited the volume of exogenously stimulated (secretin and CCK) pancreatic secretion and pancreatic bicarbonate and amylase secretion only on Day 2 after administration. Lanreotide did not significantly affect exogenously stimulated biliary secretion of bilirubin. Meal-stimulated secretion of amylase and bilirubin (AUC values) were significantly inhibited by lanreotide only on Day 2.

Somatostatin inhibits gastric acid secretion by inhibiting gastrin and by direct action on parietal cells. Lanreotide dose-dependently increased median gastric pH values and increased the duration of decreased acidity when given as a 24-hour infusion.

The human digestive tract and pancreas contain a large number of cells that secrete somatostatin. Somatostatin inhibits intestinal secretion of calcium, glucose, galactose, glycerol, fructose, xylose, lactose, amino acids, triglycerides, and water.

When studied, as expected, lanreotide significantly reduced PGE1-stimulated jejunal secretions of water, sodium, potassium, and chloride.

Somatostatin reduces blood flow to the small intestine. It inhibits mesenteric blood flow and restricts portal flow by constricting splanchnic blood vessels. Some studies have shown that GH and IGF-1 increase glomerular filtration rate (GFR) and renal plasma flow in healthy volunteers, and the somatostatin analogue octreotide decreased GFR in insulin-dependent diabetics and acromegalics. Three studies investigated the effects of lanreotide on renal and splanchnic blood flow in healthy subjects.

These studies showed that lanreotide decreases SMA and portal venous flow but has no effect on renal blood flow.

Inhibition of gallbladder contractility is a known effect of the drug class. The somatostatin analogue octreotide inhibits gallbladder contractility and facilitates formation of gallstones; approximately 18% of patients treated chronically develop either gallbladder sludge or stones. As expected, a single injection of lanreotide also significantly inhibited basal and post-prandial gallbladder contraction. Somatostatin inhibits the release of thyroid-releasing hormone (TRH) in humans. This effect is readily observed in patients who are hypothyroid or who undergo stimulation with TRH. The three studies which investigated the effects of lanreotide on thyroid parameters confirmed that lanreotide administered as continuing infusion significantly inhibited nocturnal TSH in healthy volunteers and when administered repeatedly slightly affected TSH values compared to baseline in acromegalic patients. Somatostatin inhibits prolactin secretion. In cultured prolactinomas, this inhibition appeared to be mediated by the somatostatin receptor (SSTR) 5 receptor, but not the SSTR2 receptor. Prolactinomas appear to express only SSTR1 and SSTR5, and SSTR5 expression is correlated with prolactin regulation. Prolactin levels were measured in two studies conducted with lanreotide. In both of these studies, lanreotide treatment reduced prolactin levels.

Although acute administration of somatostatin strongly inhibits exocrine pancreatic secretions, divergent results have been published after prolonged treatment. Evidence from studies with the SST analogue octreotide suggests that the degree of inhibition of pancreatic secretion may decrease with continuing treatment. Inhibition of pancreatic enzyme secretion persisted after six days of treatment with the somatostatin analogue octreotide, but the degree of inhibition subsided from 80% to about 60% of control values, indicating an escape from the inhibitory effect of octreotide on CCK-stimulated enzyme secretion. A similar trend has been seen with acute and chronic administration of lanreotide.

Laboratory investigations of acromegalic patients treated with Somatuline Autogel in clinical studies show that the percentage of patients with putative antibodies at any time point after treatment is low (<1% to 4% of patients in specific studies whose antibodies were tested). The antibodies did not appear to affect the efficacy or safety of Somatuline Autogel.

In Study 726, development of anti-lanreotide antibodies was assessed using a radioimmunoprecipitation assay. In patients with enteropancreatic NETs receiving Somatuline Autogel, the incidence of anti-lanreotide antibodies was 3.7% (3 of 82) at 24 weeks, 10.4% (7 of 67) at 48 weeks, 10.5% (6 of 57) at 72 weeks, and 9.5% (8 of 84) at 96 weeks. Assessment for neutralizing antibodies was not conducted.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Somatuline Autogel with the incidence of antibodies to other products may be misleading.

Clinical pharmacokinetics

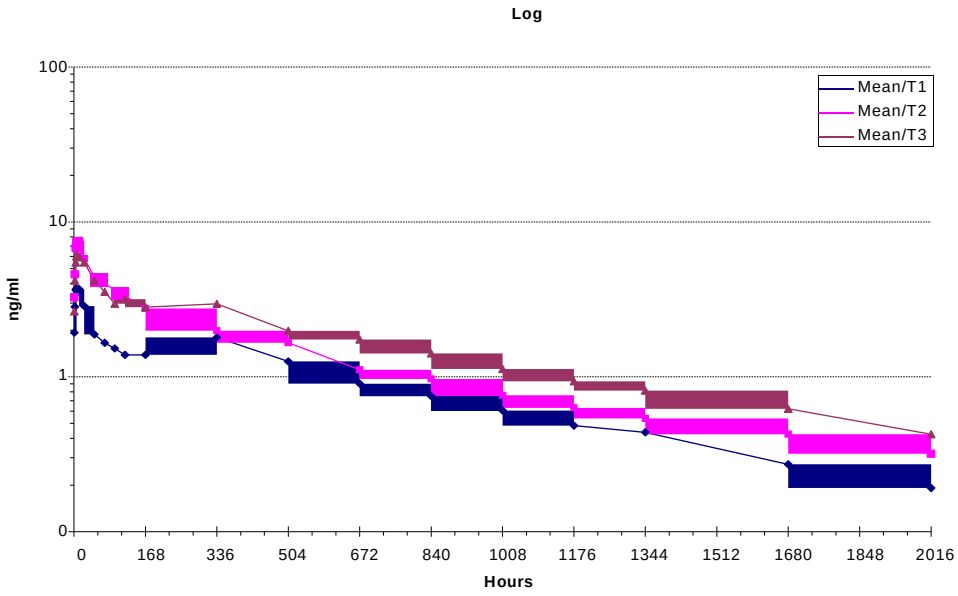
Pharmacokinetics of Somatuline Autogel in Healthy Volunteers

Descriptive pharmacokinetic of lanreotide after Autogel deep subcutaneous administration was studied in healthy volunteers after a single administration. Results from this study show that the

lanreotide release profile approximates log-linear following deep sc administration (Figure 3).

Studies in healthy elderly subjects receiving the immediate-release formulation of lanreotide showed an 85% increase in half-life and a 65% increase in mean residence time (MRT) of lanreotide compared to healthy young volunteers. However, there was no change in either AUC or C_{max} of lanreotide in elderly subjects compared to healthy young subjects.

Figure 3. Mean, overlaid, plasma concentration-time profiles of lanreotide (ng/mL) after deep sc administration of Somatuline Autogel T_1, T_2 and T_3 (dose = 60, 90 and 120 mg, respectively)



Standard pharmacokinetic parameters monitored in this study following deep sc administration of Somatuline Autogel to healthy volunteers are summarised below.

Table 10. Pharmacokinetic parameters following a single deep subcutaneous administration of Somatuline Autogel 60, 90 and 120mg to healthy volunteers

Parameter	60 mg (N=13)			90 mg (N=13)			120 mg (N=12)		
	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%
C_{max} (ng/mL)	4.246	1.934	45.55	8.391	4.915	58.57	6.785	3.641	53.66
AUC_t (ng/mL/h)	1634.61	435.19	26.62	2453.78	816.66	33.28	2984.81	1024.70	34.33
AUC_∞ (ng/mL/h)	1904.98	564.09	29.61	2984.35	1214.04	40.68	3552.26	947.33	26.67
$t_{1/2}$ (h)	664	455	68.52	860	431	50.12	816	334	40.93
t_{max} (h)*	8 (4 to 336)	--	--	12 (4 to 336)	--	--	7 (2 to 48)	--	--
t_{lag} (h)	<1.0	0.0	--	<1.0	0.0	--	<1.0	0.0	--
MRT (h)	940.62	462.83	49.20	1009.87	568.17	56.26	1102.13	469.61	42.61
MAT (h)	939.78	463.00	49.27	1009.11	568.28	56.31	1101.29	469.49	42.63
F (%)	83.25	34.56	41.51	78.14	25.87	33.11	80.87	24.18	29.90

* = median and range in parenthesis

Both AUC_t and AUC_∞ increased with the dose; C_{max} increased from 60 to 90 mg but at 120 mg an intermediate value was obtained. The high inter-subject variability observed for this parameter could explain why a dose relationship was not observed for C_{max}. Some variability was also observed in t_{max} ranging between 2 and 48 hours, except in two volunteers who showed an unexpected value of 336 h. No important differences were observed in the median values obtained for these parameters (7 to 12 hours). The other parameters $t_{1/2}$, t_{lag}, MRT (Mean Residence Time), MAT (Mean Absorption Time) and F% showed similar values in the three dose groups. Mean $t_{1/2}$ ranged from 664 to 860 hours (28 to 36 days) and bioavailability ranged from 78% to 83%.

Pharmacokinetics of Somatuline Autogel in Patients with Acromegaly

The primary pharmacokinetic results for Somatuline Autogel are derived from a randomised, parallel-group, double-blind, single-center study that evaluated the pharmacokinetic profile of Somatuline Autogel administered at fixed doses of 60, 90, and 120 mg four times every 28 days in 18 patients with active acromegaly.

Following a single dose, the pharmacokinetics of Somatuline Autogel were dose-independent in the dose range 60 to 120 mg. Dose proportionality was observed in the pharmacokinetic parameters $C_{min,1}$, C_{max} and AUC_τ as shown in the table below.

Table 11. Comparative Mean (± SD) Pharmacokinetic Parameters Following a First Single Dose of Somatuline Autogel of 60, 90 and 120 mg to Patients with Acromegaly

Parameter (units)	60mg			90mg			120mg			p
	Mean	SD	N	Mean	S.D.	N	Mean	S.D.	N	
T_{max} [(1)] (d)	0.25 (0.17-0.98)		6	0.25 (0.25-1.00)		5	0.98 (0.24-0.99)		5	0.433
C_{max} ($ng.ml^{-1}$)	1.650	0.623	6	3.543	2.546	5	3.053	0.932	5	0.694 [(2)]
C_{min} [1] ($ng.ml^{-1}$)	0.725	0.191	6	0.973	0.199	5	1.406	0.306	6	0.699 [(2)]
$AUC\tau$ ($ng.ml^{-1}.d$)	22.27	6.42	6	37.29	14.23	5	48.49	15.36	6	0.864 [(2)]

[(1)] For this parameter, the median and range values were used
[(2)] p value corresponding to pharmacokinetic parameters normalized by dose

Somatuline Autogel exhibited linear pharmacokinetics after repeated doses over the range of 60 to 120 mg administered once every 28 days (Table 12). Pharmacokinetic parameters $C_{min,ss}$, $C_{max,ss}$ and AUC_τ increased in a dose-dependent linear manner. During the dosing interval, average steady state concentrations (C_{avg}) of 2.457, 3.040 and 4.523 $ng \cdot mL^{-1}$ were observed for the 60, 90 and 120 mg dose levels, respectively.

Table 12. Comparative Mean (± SD) Steady-State Pharmacokinetic Parameters Following Four Doses of Somatuline Autogel 60, 90 and 120 mg to Patients with Acromegaly

Parameter (units)	60mg			90mg			120mg			p
	Mean	SD	N	Mean	S.D.	N	Mean	S.D.	N	
$T_{max, ss}$ [1] (d)	84.62 (84.17-85.99)		4	84.29 (84.17-85.99)		6	84.66 (84.33-85.97)		6	0.615 [2]
$C_{max , ss}$ ($ng.ml^{-1}$)	3.821	0.509	4	5.694	1.672	6	7.685	2.470	6	0.974 [2]
$C_{min , ss}$ ($ng.ml^{-1}$)	1.822	0.304	4	2.511	0.882	6	3.762	1.012	6	0.721 [2]
AUCτ ($ng.ml^{-1}.d$)	68.79	8.53	4	85.11	17.10	6	126.66	27.66	6	0.279 [2]
C_{avg} ($ng.ml^{-1}$)	2.457	0.305	4	3.040	0.611	6	4.523	0.988	6	0.289 [2]

[1] For this parameter, the median and range values were used
[2] p value corresponding to pharmacokinetic parameters normalized by dose

Peak-trough fluctuation during the dosing interval was dose-independent in the dose range 60 to 120 mg, with values of 81%, 108% and 86% for the 60, 90 and 120 mg doses, respectively.

Four consecutive Somatuline Autogel administrations produced a slight accumulation independent of the dose level, with a mean accumulation index of approximately 2.7. This accumulation result is not unexpected considering the long half-life of Somatuline Autogel.

Following a single dose of Somatuline Autogel 60, 90 or 120 mg in Study 717, C_{min1} increased with lanreotide dose. The minimum serum levels after at least four consecutive lanreotide administrations at the same dose (steady-state) also increased with dose. Although the increase in $C_{min,ss}$ was slightly less than proportional to the dose for comparison of the 120 mg and the 60 mg doses in this study, no statistically significant differences by dose could be demonstrated when normalized by dose ($C_{min\ ss}$/D). These results indicate that Somatuline Autogel exhibited linear pharmacokinetics in acromegalic patients over the range of 60 to 120 mg after four consecutive doses of Somatuline Autogel once every 28 days. Moderate accumulation of lanreotide in the body was also observed during this study at all dose levels, with mean accumulation indices (R_{ac}) of 2.6, 3.2 and 2.8 for the 60, 90 and 120 mg doses, respectively.

The mean C_{max} values following initial dosing with Somatuline Autogel were 2- to 4-fold higher than mean minimum serum levels after first Autogel administration (C_{min1}), indicating that no initial burst effect is produced with this formulation for the three dose levels tested (60, 90 and 120 mg). Consistent observations were made after multiple deep s.c. injections.

Pharmacokinetic data from studies evaluating the use of extended dosing intervals of Somatuline Autogel 120 mg every 6 or 8 weeks, demonstrated mean steady state C_{min} values between 1.6 and 2.3 ng/mL for the 8 and 6 week treatment intervals, respectively. The median minimum effective serum concentration of lanreotide required to reduce GH levels to ≤ 2.5 ng/mL ranged from 0.95 to 1.13 ng/mL.

Studies evaluating the use of extended dosing intervals of Somatuline Autogel 120 mg every 6 or 8 weeks were not conducted in patients with moderate or severe hepatic or renal impairment. There are no pharmacokinetic data available regarding the use of Somatuline Autogel 120 mg every 6 or

8 weeks in patients with moderate or severe hepatic or renal impairment.

Pharmacokinetics of Somatuline Autogel in Patients with enteropancreatic NETs

Individual PK parameters (post hoc Empirical Bayes Estimates) were obtained from a population PK model including 290 NETs patients. Descriptive statistics on individual PK parameter estimates are shown in Table 13.

Table 13. Summary Statistics of Lanreotide Pool PK Model Parameters

	CL/F (L/day)[a]	V/F (L)	K_A (day^{-1})	$t_{1/2}$ K_A (days)
Somatuline Autogel120 mg (N=298)				
Mean (SD)	519 (129)	26.3 (30.2)	0.0174 (0.00900)	49.8 (28.0)
Geometric mean	503	20.7	0.0156	44.4
Median	504	18.3	0.0157	44.3
5th and 95th percentiles	327-743	13.1-85.9	0.00750-0.0358	19.3-93.0

CL/F=apparent total plasma clearance; V/F=apparent volume of distribution; K_A=constant of absorption; $t_{½}K_A$=absorption half life

a Only 290 subjects provided at least one concentration and were included in the PK model building. However, the PK parameters were simulated for the whole population (N=298)

In addition, Somatuline Autogel 120 mg exposure parameters after a single dose and at steady state were simulated from the model. Summary statistics are presented for the single dose in Table 14 and for steady state in Table 15.

Table 14. Summary Statistics of Derived Somatuline Autogel 120 mg Exposure Parameters After a Single Dose

	AUC_{0-28} (ng*day/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)
Mean (SD)	88.6 (40.1)	7.49 (7.58)	2.40 (0.930)	3.44 (1.57)
Geometric Mean	80.1	5.73	2.20	3.11
Median	83.8	5.39	2.38	3.24
5th and 95th percentiles	38.5 to 162	2.17 to 20.6	1.14 to 4.05	1.48 to 6.33

AUC=Area under the curve over the dosing interval (4 weeks); C_{max}=maximum concentration; C_{min}=concentration at the end of a dosing interval; C_{avg}=average concentration over the dosing interval (4 weeks); SD=standard deviation

Table 15. Summary Statistics of Derived Somatuline 120 mg Exposure Parameters at Steady State

	AUC_{0-28} (ng*day/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)
Mean (SD)	239 (64.8)	13.9 (7.44)	6.56 (1.99)	8.64 (2.36)
Geometric mean	232	12.8	6.23	8.35
Median	231	11.9	6.49	8.41
5th and 95th percentiles	158-358	7.69-25.5	3.53-9.99	5.49-12.9

AUC=Area under the curve over the dosing interval (4 weeks); C_{max}=maximum concentration; C_{min}=concentration at the end of a dosing interval; C_{avg}=average concentration over the dosing interval (4 weeks)

Rapid initial release was seen with mean C_{max} values of 7.49 ± 7.58 ng/mL reached within the first day after a single injection. Steady-state concentrations were reached after 4 to 5 injections of Somatuline Autogel 120 mg every 4 weeks and were sustained up to the last assessment (up to 96 weeks after the first injection). At steady state, the mean C_{max} values were 13.9 ± 7.44 ng/mL and the mean trough serum levels were 6.56 ± 1.99 ng/mL. The mean apparent terminal half-life was 49.8 ± 28.0 days.

Excretion and Metabolism

Two studies examined the excretion of lanreotide. When lanreotide was given as a single sc dose of 3 mg, less than 1% of the administered dose was recovered in urine, and renal clearance was <1% of total plasma clearance. When lanreotide was given by sc infusion, the fraction of lanreotide excreted in the urine at steady state was 1% to 5% for a dose of 0.75 mg/day. Data for fecal excretion were collected in this study and less than 0.5% of the administered dose was recovered over a 24 hour period at steady state.

Therefore, urinary and fecal excretion represents only a small fraction of the total dose administered. This suggests that lanreotide is probably metabolised extensively in the gastrointestinal tract after biliary excretion.

Intrinsic Factor Pharmacokinetic Studies

Pharmacokinetic studies have been conducted with lanreotide in patients with chronic renal failure, hepatic failure and in elderly subjects.

Table 16. Summary of Lanreotide's Pharmacokinetic Parameters* in Special Populations

	C_{max} (ng/ml)	**$t_{½}$ (h)**	**$AUC_{0\text{-}inf}$ (ng/ml.h)**	**Clearance (l/h.kg)**	**Volume of distribution (l/kg)**
Geriatric Patients					
Single dose mean Study E-92-52030-012	48.75	1.74	29.17	0.269	0.200
Hepatic Insufficiency					
Single dose mean **Mild to Moderate** Study E-92-52030-013	28.74	1.66	20.02	0.362	0.322
Moderate to Severe Study E-38-52030-701	34.394	2.998	30.090	0.237	0.349
Severe Chronic Renal Insufficiency					
Single dose mean Study E-92-52030-011	307.45	2.39	62.95	0.138	0.110

*Lanreotide was administered intravenously as the immediate release formulation

Differences were observed in the pharmacokinetics of lanreotide in renal, hepatic, and geriatric populations. No gender differences were found in PK parameters.

No gender differences were found in PK parameters.

Extrinsic Factor Pharmacokinetic Studies

The potential for interference between lidocaine and lanreotide was studied. The binding of lidocaine in serum varied from 78.84% to 68.28% when the concentration increased from 4 to 20 μM. Binding remained unchanged in the presence of 400 nM of lanreotide. This confirms that lanreotide, given its moderate total binding, its average affinity for acid alpha-1 glycoprotein (65000 M^{-1}), and its very low therapeutic serum concentration (-100 nM), cannot displace other drugs bound to this protein.

The potential for drug-drug interactions of lanreotide between Somatuline Autogel and cyclosporin and vitamin K has been evaluated. Lanreotide decreased the bioavailability of oral cyclosporin by approximately 20%. No significant interaction with vitamin K was observed.

Literature comparisons of lanreotide with Sandostatin and Somatostatin UCB show that the principal pharmacodynamic interaction that may occur is the inhibition of glucagon secretion which may lead to the onset of hypoglycemia in treated diabetic patients, notably insulin-dependent patients. Thus, the insulin requirements in insulin-dependent diabetic patients may be reduced.

MICROBIOLOGY

Not applicable

TOXICOLOGY

An immediate-release formulation (IRF) of lanreotide, administered either by sc injection or as an iv infusion was used for most of the toxicology studies. This allowed considerably higher doses to be achieved than would have been possible with the Autogel formulation.

Single Dose Toxicity Studies

Table 17: Summary of lanreotide single dose toxicity studies

Species	Route	Dose	No effect dose (mg/kg)	Minimal effect dose (mg/kg)	LD50 (mg/kg)
Mouse	i.v	0.8, 30, 100, 120, 135, 150, 180 mg/kg	<30	30	120-135
Rat	i.v.	3, 6, 24, 48, 60, 75 mg/kg	3	>6	>48
Mouse	s.c.	0.8, 600, 900, 1200 mg/kg	<600	600	>1200
Rat	s.c.	0.8, 1500 mg/kg	<1500	1500	>1500

The results of the single dose i.v. and s.c. studies indicated that both rodent species were able to tolerate large doses of lanreotide. There was no evidence of organ specific toxicity.

Repeat Dose Toxicity Studies

Table 18: Summary of lanreotide repeat dose toxicity studies

Species	Route	Duration	Doses (mg/kg/day)
Mouse	s.c.	5 days	0.8
Mouse	s.c.	13 weeks	0, 10, 30, 60
Mouse	s.c.	13/20 weeks	0, 0.5, 5*, 1 od 0.1*, 0.5 bid (*0.1 changed to 5 Weeks 8-20)
Rat	s.c.	6 weeks	0, 0.004, 0.04, 0.2
Rat	s.c.	13 weeks	0, 0.5, 1 od 0.1, 0.5 bid
Rat	s.c.	26 weeks	0, 0.2, 1.0, 5.0 (3.0, 2.0)
Rat	i.v. infusion	14 days	0, 1, 5, 20
Dog	s.c.	6 weeks	0, 0.004, 0.04, 0.2
Dog	i.v. infusion (dose finding)	14 days	2.5, 5.0, 10 (6 days) 20, 25
Dog	i.v. infusion	45 days	0, 0.4, 4.0, 10
Dog	i.m.	26 weeks	1.00-1.62, 3.35-4.98, 6.26-9.95 mg/kg once every 2 weeks.

The toxicological effects associated with repeated subcutaneous, intramuscular and intravenous administrations were assessed in mice and/or rats and dogs (see Table above). Chronic toxicity was assessed in the rat and in the dog. The results of these studies revealed no evidence of target organ toxicity. Inhibition of growth rates observed at high doses was considered to be secondary to lanreotide's recognized pharmacologic effect, inhibition of growth hormone secretion. Similarly, lanreotide-associated reductions in serum concentrations of some hormones were considered to be extensions of the pharmacologic effect. Continuous infusion of lanreotide to dogs for up to 45 days was associated with dose-related testicular immaturity in males. Control animals also had immature testicles but the degree of immaturity appeared to increase in a dose- related fashion and was consistent with the general growth retardation of lanreotide treated animals.

With the exception of dose-related irritation at the site of injection, lanreotide was well tolerated by all test species and the results indicate little, if any, potential for chronic administration of the drug in humans to produce target organ toxicity.

Chronic Toxicity Studies

Table 19: Summary of lanreotide chronic toxicity studies

Species	Route	Duration	Doses (mg/kg/day)
Rat	s.c.	24 months	0, 0.008, 0.040, 0.120
Dog	s.c.	24 months	0, 0.008, 0.040, 0.120

The chronic toxicity of subcutaneously administered lanreotide was assessed in a 24 months study in rats. The results of this study were similar to those of shorter-term repeated dose studies in that there was no evidence of systemic, organ specific toxicity. Further, there was no evidence that lanreotide influenced the incidence or rate of onset of spontaneously occurring neoplasms in this strain of rats.

Chronic toxicity (24 months) was also assessed in dogs. The results of this study corroborated the absence of significant systemic toxicity observed in dogs after shorter-term repeated dose studies.

Genotoxicity

Table 20: Summary of *In Vivo* and *In Vitro* Mutagenicity Studies

Test	Lanreotide Concentration	Organism/ Cell Source	Metabolic Activation S9
Non-mammalian *in vitro* assays			
AMES test	1.6 to 5000 mcg/plate	TA 1535 TA 100 TA 1537 TA 98 WP2 uvrA	(+/-) (+/-) (+/-) (+/-) (+/-)
Mammalian cell *in vitro* assays			
Mouse lymphoma assay	100 - 1200 mcg/ml	Mouse lymphoma cells	(+/-)
Chromosomal aberration assay	393.7 - 2000 mcg/ml	Human lymphocytes	(+/-)
***In vivo / in vitro* Mutation frequency and DNA synthesis and repair assays**			
Induction of gene mutations in liver and bone marrow tissue	120 or 180 mg/kg/day subcutaneous	Male CD_2-lacZ80/HazfBRstrain mice	NA
Mammalian cell *in vivo* assays (PO)			
Micronucleus test	6.25, 12.5, 25 mg/k/day intravenous	Male and female Swiss Ico: OF1 (IOPS Caw) mice	NA

The standard battery of genotoxicity tests were performed. In this set of studies, no positive

results were obtained.

Carcinogenicity

A two-year mouse carcinogenicity study was conducted wherein males and females were administered lanreotide once daily by subcutaneous injection at 0.5, 1.5, 5, 10 and 30 mg/kg/day. Reduced survival was observed at 30 mg/kg/day in males and females and was related to the presence of masses at subcutaneous injection sites (increased incidence of fibrosarcomas and malignant fibrous histiocytomas). No systemic neoplastic changes were observed.

A two-year rat carcinogenicity study was conducted wherein males and females were administered lanreotide once daily by subcutaneous injection at 0.1, 0.2, and 0.5 mg/kg/day. Survival rate was comparable in male treated groups compared to male control groups. In females, survival rate tended to be higher at all dose levels. No systemic neoplastic changes were observed. At injection sites of male and female rats treated with 0.5 mg/kg/day lanreotide, an increased incidence of fibrosarcomas and malignant fibrous histiocytomas was observed.

The increased incidence of subcutaneous tumours at injection sites is likely due to the increased dose frequency in animals (daily). Considering that monthly dosing is recommended in humans, these findings may not be clinically relevant. Exposure multiples (ratio of animal AUC to human AUC) were not calculated as systemic tumours were not observed.

Reproductive Toxicity

The high dose somatostatinergic effects of lanreotide on the secretion of pituitary hormones can be expected to cause perturbations of reproduction. The effects of lanreotide on mating behaviour and reproductive performance were assessed in male and female rats by administering the drug by the s.c. and/or i.m. routes.

Although administered at doses sufficiently high to reduce growth rates of both males and females of the F_0 generation neither mating behaviour nor reproductive performance were adversely affected. The behavioural and reproductive characteristics of the F1 and F2 generations were similarly unaffected by administration of lanreotide to the parental generations.

Teratological potential was assessed by daily administering s.c. doses of lanreotide (0, 100, 450, or 2000 mcg/kg) to pregnant rats (from gestation day 6 to 15) and rabbits (from gestation day 6 to 18). The doses were selected on the basis of preliminary dose range finding studies, at doses up to and including 5000 mcg/kg/day, which are included within the documentation. Female rats administered the 2000 mcg/kg dose exhibited decreased weight gains but there was no evidence of either foetal toxicity or teratological anomalies. In rabbits, all dosed groups had reduced body weight gains and there was evidence of foetal toxicity (increased post implant loss in the 450 and 2000 mcg/kg groups) but no evidence of either soft tissue or skeletal anomalies.

Local Tolerance

Specific tolerance studies with the Somatuline Autogel formulation have been conducted, and are summarized below.

Table 21: Summary of lanreotide local tolerance studies

Species/ Strain	Method of Administration	Doses (mg/kg)
Rabbit/ NZW	Single i.m.	60 mg per animal
Rabbit/ NZW	Repeated i.m.	10 mg per animal/ 4 weeks
Rabbit/ NZW	Single s.c.	60 mg per animal
Rabbit/ NZW, Monkey/ Cynomolgus, Minipig/ Gottingen	Single s.c.	60 mg per animal
Rabbit	Repeated s.c.	10 mg per animal/ 4 weeks

Local tolerance testing involved following animals for up to 150 days after s.c. or i.m. injection, in single and multiple dose studies. Local tolerance was adequate to support the prolonged intermittent use of Somatuline Autogel in patients. Findings can be summarized as follows. The local tolerance on i.m. and s.c. injection was acceptable. Local tolerance studies of the Autogel formulation proposed for marketing showed a locally restricted response with development of a fibrous capsule at the injection site. The response was not severe and is likely to be similar to the effects of injecting other biocompatible materials. No general adverse reactions were observed and there was no difference in local tolerance after multiple doses compared to single injections.

Immunotoxicity

Provision was made to assess the potential to adversely affect lymphocytes, macrophages and natural killer cells during the course of a 45-day continuous i.v. infusion toxicity study in beagle dogs. No effects were found at doses of 0.4, 4 or 10 mg/kg to indicate that lanreotide has any potential to modify the selected immunotoxicity end-points.

Lanreotide is a small peptide whose molecular weight is below the approximate 10000 minimum for antigenicity independently of any haptenic function. Neither modifications of the hematology parameters nor lesions of the lymphoid organs, which may be indicative of immunostimulation, were observed in treated rats and dogs.

Blood samples obtained from rats after 26 weeks and 24 months of daily s.c. administration of lanreotide at doses of 0, 8, 40 and 120 mcg/kg/day tested negative for anti-lanreotide antibodies. Thus no evidence was obtained in these studies to conclude that lanreotide has any immunogenic potential when repeatedly administered to rats for prolonged periods.

REFERENCES

1. Phase II, multi-centre, randomised, double-blind study, in acromegalic patients evaluating the efficacy and safety of a single deep subcutaneous administration of lanreotide autogel (60, 90, or 120 mg) versus placebo, followed by a single-blind fixed dose phase evaluating the pharmacokinetic, pharmacodynamic, efficacy and safety profile of multiple deep subcutaneous administrations of lanreotide autogel (60, 90 & 120 mg) ending in open label dose titration phase. Study E28 52030 717. Data on file. Beaufour Ipsen Pharma 2004.

2. Lanreotide in Metastatic Enteropanceratic Neuroendocrine Tumors, Caplin M, et al. , N Engl J Med 371;3, July 17, 2014.

PART III: CONSUMER INFORMATION

SOMATULINE® AUTOGEL®
lanreotide injection
60, 90, 120mg lanreotide (as acetate)/unit (syringe)

This leaflet is part III of a three-part "Product Monograph" published when Somatuline® Autogel® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Somatuline Autogel. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Somatuline® Autogel® is recommended for :
- the treatment of acromegaly.
- the treatment of neuroendocrine tumors from the gastrointestinal tract or the pancreas that cannot be completely removed by surgery

What it does:
Somatuline Autogel is a long-acting formulation of lanreotide that lasts for several weeks. Lanreotide is similar to the naturally occurring hormone somatostatin. Lanreotide lowers the levels of hormones in the body such as GH (growth hormone) and IGF-1 (insulin-like growth factor-1) and inhibits the release of some gastrointestinal hormones and intestinal secretions. Additionally it has an effect on some neuroendocrine tumors by delaying growth.

When it should not be used:
Somatuline Autogel should not be used if you:
- have previously been allergic to lanreotide or any other drug like somatostatin;
- have untreated gallstones

What the medicinal ingredient is:
lanreotide acetate

What the important nonmedicinal ingredients are:
The only excipients are water for injection and glacial acetic acid (for pH adjustment).

What dosage forms it comes in:
Somatuline Autogel is packaged in a sterile, pre-filled syringe fitted with an automatic safety system, ready to be injected. It is available in three strengths of 60 mg, 90 mg and 120 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Treatment with Somatuline Autogel may:
- cause loss of blood sugar control in diabetic patients
- cause gall stone
- affect (lower) the blood level of cyclosporine

BEFORE you use Somatuline Autogel talk to your doctor or pharmacist if:
- you are diabetic
- you have or have had liver problems
- you have or have had kidney problems
- you have or have had heart problems
- you have or have had gall bladder problems
- you are pregnant, planning to become pregnant
- you are breast-feeding

Somatuline Autogel is not recommended for patients under 16 years of age.

INTERACTIONS WITH THIS MEDICATION

Before and during treatment with Somatuline Autogel, tell your doctor of pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you can buy without prescription, and herbal products.

Drugs that may interact with Somatuline Autogel include:
- cyclosporine
- bromocriptine

,

PROPER USE OF THIS MEDICATION

Usual Adult Dose:
If you have acromegaly, the recommended starting dose is an injection of Somatuline Autogel 90 mg. You will normally be given one injection every 28 days. Your doctor may change the dose or the length of time between your injections, depending on how your symptoms and hormones are responding to the product. Your doctor will tell you how long you need to receive Somatuline Autogel.

If you have an enteropancreatic neuroendocrine tumor , you will receive a Somatuline Autogel 120 mg injection every 4 weeks for as long as your doctor recommends.

Somatuline Autogel is given as a deep subcutaneous (deep under the skin) injection by a healthcare professional or a properly trained person. You may give yourself an injection if you have been properly trained and are able to follow the Instructions for Administration of Somatuline Autogel.

INSTRUCTIONS FOR ADMINISTRATION OF SOMATULINE AUTOGEL
FOLLOW THESE INSTRUCTIONS CAREFULLY.

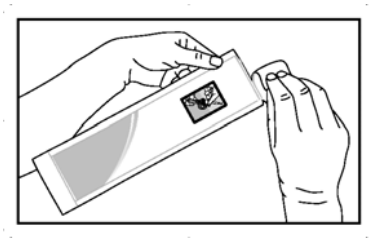
1. Remove Somatuline Autogel from the fridge 30 minutes prior to administration. Keep pouch sealed until just prior to injection.

2. Before opening the pouch, check that it is intact and that the medication has not expired. The expiration date is printed on the outer carton and the pouch. DO NOT USE IF THE

MEDICATION HAS EXPIRED OR IF THE LAMINATED POUCH IS DAMAGED IN ANY WAY.

3. Wash hands with soap and ensure there is a clean area for preparation.

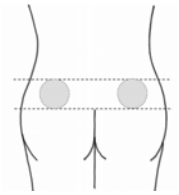
4. Tear-open the pouch and take out the pre-filled syringe.



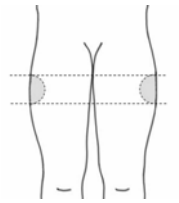
5. Select an injection site:

5a The superior external quadrant of the buttock (for injection by healthcare professional (HCP) or someone else like a trained family member or friend), or

5b The upper outer part of your thigh (if you will be injecting yourself).



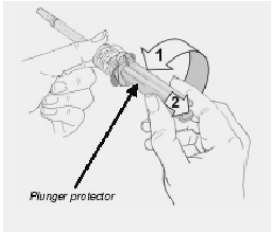
or



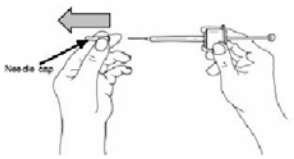
5a 5b

6. Clean the injection site without rubbing the skin excessively.

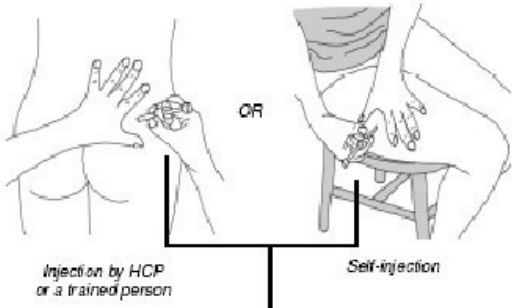
7. Twist and pull off the plunger protector and discard it.

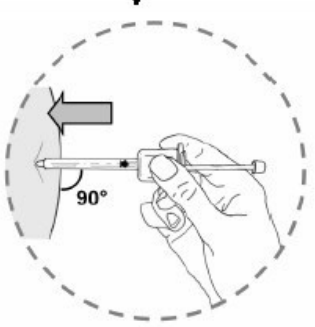


8. Remove the needle cap and discard it.

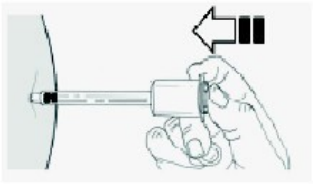


9. Hold the skin around the injection site flat using your thumb and index finger. Do not pinch, fold, or press on the skin at the injection site. Rapidly insert the needle to its full length (deep subcutaneous injection), perpendicular (90°) to the skin

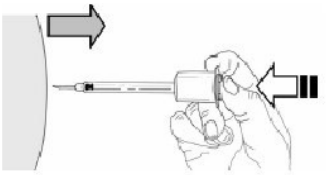




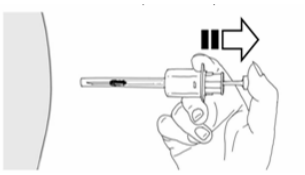
10. Slowly inject the drug**. Typically 20 seconds are needed**. Inject the full dose until the plunger cannot be depressed any further. At this point, you will hear a "click". Maintain pressure on the plunger with your thumb to avoid activation of the automatic safety system.



11. Without releasing the pressure on the plunger, withdraw the needle from the injection site.



12. Then release pressure on the plunger. The needle will automatically retract into the needle guard where it will be locked permanently.



13. Apply gentle pressure to the injection site with a dry cotton ball or sterile gauze to prevent any bleeding. Do not rub or massage the injection site after administration.

14. Properly dispose of the used syringe.

Overdose:
In case of drug overdose, contact your doctor, or a poison control centre, or go to the emergency room of the hospital near you.

Missed Dose:
As soon as you realise that you have missed an injection, contact your doctor. They will give you advice about the timing of your next injection. Do NOT give yourself extra injections to make up for the one that you have forgotten.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Somatuline Autogel can have side effects: Very common side effects include:
- diarrhea (loose stools)
- gall bladder stone (a severe pain in the abdomen with nausea and vomiting)
- flatulence (passing gas)
- abdominal pain
- weight loss
- low red blood count (anemia)
- decreased heart rate (bradycardia)

Common side effects include:
- abnormally low or high blood sugar levels
- loss of appetite
- indigestion
- nausea and vomiting
- constipation
- fatty stools
- dizziness
- headache
- tiredness or decreased energy
- injection site reaction
- hair loss
- muscle pains

Uncommon side effects include:
- worsening of diabetes
- acute inflammation of the pancreas (acute pancreatitis)
- allergic reactions
- hard swelling of the injection site, and rarely a persistent hard swelling

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	**In all cases**
Very common (Occurs in more than 1:10 patients)	Abdominal pain	yes	
	Diarrhoea or loose stools	yes	
	Formation of gallstones in the gall bladder with symptoms such as severe pain in the abdomen which may last for hours, accompanied by nausea and vomiting.		yes
	Headache	yes	
	Vomiting	yes	
Common (Occurs in between 1:10 and 1:100 patients)	Injection site reaction	yes	
	Decreased heart rate (bradycardia)		yes
Uncommon (Occurs in between 1:100 and 1:1000 patients)	Acute pancreatitis (inflammation of the pancreas causing severe stomach pain)		yes
	Allergic Skin Reactions	yes	
Post-marketing	Severe allergic reactions (swollen face; tightness in chest, shortness of breath or wheezing; faintness due to a drop in blood pressure)		yes

This is not a complete list of side effects. For any unexpected effects while taking Somatuline Autogel, contact your doctor or pharmacist.

HOW TO STORE IT

Store Somatuline Autogel at 2°C-8°C in a refrigerator in its original package. Do not freeze. Keep out of the reach and sight of children. Do not use after the expiry date shown on the labels and box.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Report Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at: www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Ipsen Biopharmaceuticals Canada Inc. at 5060 Spectrum Way, Mississauga, ON L4W 5N5 www.ipsencares.ca or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharm Ltd.
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