

PRODUCT MONOGRAPH

Pr **SOMATULINE[®] AUTOGEL[®]**

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

Antigrowth hormone; ATC Code: H01C B03

Sponsor:

Ipsen Biopharm Limited
Unit 9, Ash Road
Wrexham Industrial Estate
Wrexham
LL13 9UF
United Kingdom

Distributed in Canada by:

EMD Serono, A Division of EMD Inc., Canada
An Affiliate of Merck KGaA, Darmstadt, Germany
200-2695 North Sheridan Way
Mississauga, ON L5K 2N6
Canada

Control Number 172903

**Date of Revision:
January 30, 2015**

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS	6
DRUG INTERACTIONS	10
DOSAGE AND ADMINISTRATION	11
OVERDOSAGE	12
ACTION AND CLINICAL PHARMACOLOGY	13
STORAGE AND STABILITY	16
SPECIAL HANDLING INSTRUCTIONS	16
DOSAGE FORMS, COMPOSITION AND PACKAGING	16
 PART II: SCIENTIFIC INFORMATION	 17
PHARMACEUTICAL INFORMATION	17
CLINICAL TRIALS	18
DETAILED PHARMACOLOGY	20
MICROBIOLOGY	26
TOXICOLOGY	26
REFERENCES	32
 PART III: CONSUMER INFORMATION.....	 33

SOMATULINE® AUTOGEL®

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

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 <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

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.

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 in this indication 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.

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

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). 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).

Renal

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).

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 precaution should be exercised. Somatuline Autogel should be administered to breast-feeding women only if clearly needed.

Pediatrics (< 16 years of age): There is no experience of the use of the product in children in this indication 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

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

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 are provided from the pivotal clinical trial using Somatuline Autogel (Study 717) in 108 patients with 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 60mg, 90mg 120mg compared to placebo as investigated during the first phase of Study 717 are provided in Table 2.

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

Preferred Term	Somatuline Autogel:				Placebo (N = 25)	Total (N = 108)*
	60 mg (N = 27)	90 mg (N = 27)	120 mg (N = 29)	Overall (N = 83)		
	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 $\geq 2\%$ 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 $\geq 2\%$ 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)

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 (%)
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)
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	3 (7)	2 (3)	3 (4)	8 (7)
Weight decrease	3 (7)	3 (5)	3 (4)	9 (8)
Hypoglycaemia				
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				

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 (%)
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)
White cell and res disorders 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:

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

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

When considering the cumulative experience from the clinical trial the following adverse drug reactions are currently being considered as uncommon.

Skin and appendages disorders: allergic skin reaction

Gastrointestinal disorders: steatorrhoea

Administration site disorders: injection site nodule

Abnormal Hematologic and Clinical Chemistry Findings

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.

Post-Market Adverse Drug Reactions

Post-marketing safety experience has not identified other relevant information. Rarely post-injection episodes of malaise with signs of dysautonomia were reported. Rare cases of persisting induration at injection site were reported.

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

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).

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.

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 tumours. 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 4: Inhibition of Radioligand Binding to Human Recombinant Somatostatin Receptors (Ki)
Comparing lanreotide and Octreotide (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

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.

Pharmacokinetics

Table 5a: 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

Table 5b: 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.

Special Populations and Conditions

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

Geriatrics: 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.

Hepatic Insufficiency: In patients with hepatic impairment, an increase in volume of distribution, mean residence time, AUC, and half-life were observed. 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).

Renal Insufficiency: Lanreotide has been studied in patients with end-stage renal function on dialysis, but has not been studied in patients with mild, moderate, or severe renal 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).

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 terephthalate/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

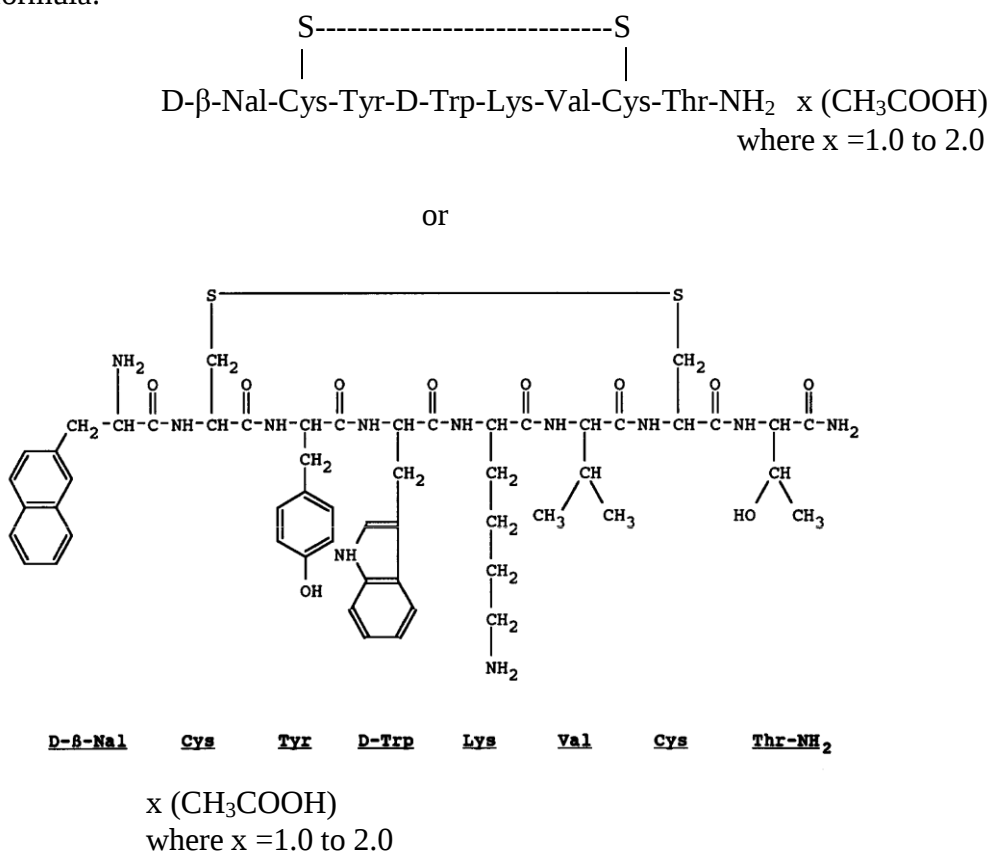
Common name: Lanreotide acetate (USAN)

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:



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

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 6. 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 $\leq$ 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 $\leq$ 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.

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.

Clinical pharmacokinetics

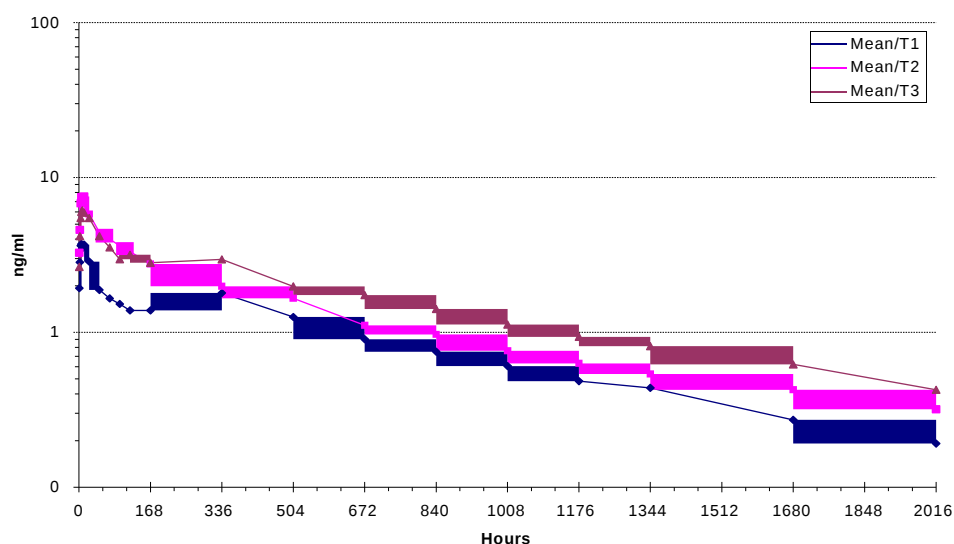
Pharmacokinetics of Somatuline Autogel in Healthy Volunteers

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 1).

Studies in healthy elderly subjects 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 1. Mean, overlaid, plasma concentration-time profiles of lanreotide (ng/mL) after deep sc administration of Somatuline Autogel T₁, T₂ and T₃ (dose = 60, 90 and 120 mg, respectively)

Log



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

Table 7. 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 8. Comparative Mean ($\pm$ 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_{τ} (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 9). 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·mL⁻¹ were observed for the 60, 90 and 120 mg dose levels, respectively.

Table 9. Comparative Mean ($\pm$ 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⁾
AUC τ (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, $C_{\min 1}$ 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 ($C_{\min 1}$), 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.

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

	C_{max} (ng/ml)	t_{1/2} (h)	AUC_{0-inf} (ng/ml.h)	Clearance (l/h.kg)	Volume of distribution (l/kg)
<i>Geriatric Patients</i>					
Single dose mean					
Study E-92-52030-012	48.75	1.74	29.17	0.269	0.200
<i>Hepatic Insufficiency</i>					
Single dose mean					
Mild to Moderate	28.74	1.66	20.02	0.362	0.322
Study E-92-52030-013					
Moderate to Severe	34.394	2.998	30.090	0.237	0.349
Study E-38-52030-701					
<i>Severe Chronic Renal Insufficiency</i>					
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 ($\sim 100 \text{ nM}$), 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 11 : 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 12 : 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 13 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 14: Summary of *In Vivo* and *In Vitro* Mutagenicity Studies

Test	Lanreotide Concentration	Organism/ Cell Source	Metabolic Activation S9
Non-mammalian <i>in vitro</i> assays			
AMES test	1.6 to 5000 mcg/plate	TA 1535	(+/-)
		TA 100	(+/-)
		TA 1537	(+/-)
		TA 98	(+/-)
		WP2 uvrA	(+/-)
Mammalian cell <i>in vitro</i> assays			
Mouse lymphoma assay	100 - 1200 mcg/ml	Mouse lymphoma cells	(+/-)
Chromosomal aberration assay	393.7 - 2000 mcg/ml	Human lymphocytes	(+/-)
<i>In vivo / in vitro</i> 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 <i>in vivo</i> 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 F₀ 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 15: 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.

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.

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.

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 or 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:

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.

Somatuline Autogel is given to you 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.

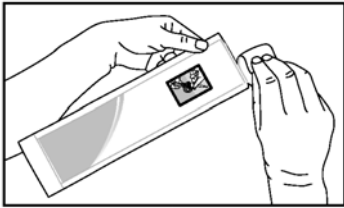
INSTRUCTIONS FOR ADMINISTRATION OF SOMATULINE AUTOGEL FOLLOW THESE INSTRUCTIONS CAREFULLY.

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.

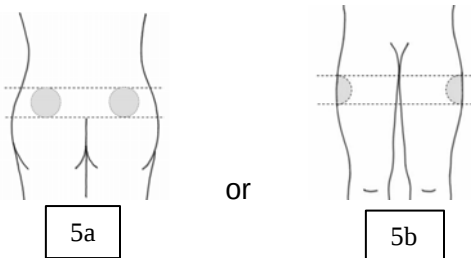
4. Tear-open the pouch and take out the pre-filled syringe.



5. Select an injection site:

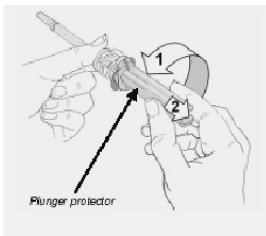
5a The superior external quadrant of the buttock (for injection by healthcare professional (HCP) or someone else like a trained family member or friend), or

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

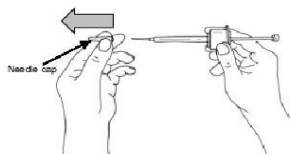


6. Clean the injection site without rubbing the skin excessively.

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

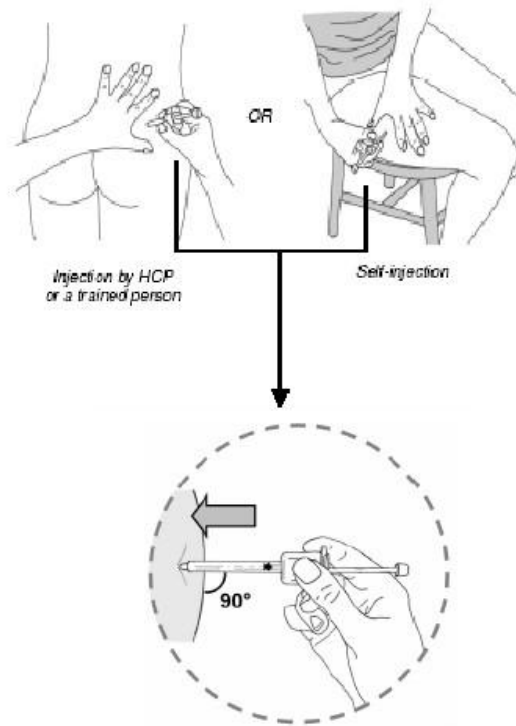


8. Remove the needle cap and discard it.

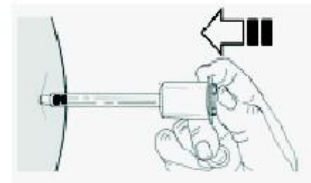


9. Hold the skin around the injection site flat using your thumb and index finger. Do not pinch, fold, or press on the skin at the

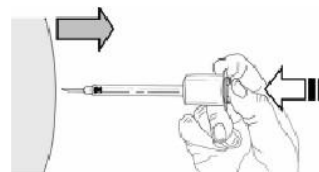
injection site. Rapidly insert the needle to its full length (deep subcutaneous injection), perpendicular (90°) to the skin



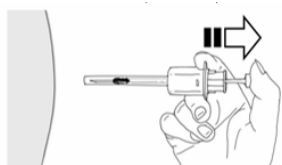
10. Slowly inject the drug. **Typically 20 seconds are needed.** Inject the full dose until the plunger cannot be depressed any further. At this point, you will hear a “click”. Maintain pressure on the plunger with your thumb to avoid activation of the automatic safety system.



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
- dizziness
- tiredness
- injection site reaction

Uncommon side effects include:

- worsening of diabetes
- acute inflammation of the pancreas (acute pancreatitis)
- fatty stools
- allergic reactions
- hair loss
- 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	
Common (Occurs in between 1:10 and 1:100 patients)	Vomiting	yes	
	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	

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 EMD Serono, A Division of EMD Inc., Canada, An Affiliate of Merck KGaA, Darmstadt, Germany at 200-2695 North Sheridan Way, Mississauga, ON L5K 2N6 www.emdserono.ca or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharm Ltd.
Last revised: January 30, 2015