PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSOMATULINE® AUTOGEL®

lanreotide injection

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

Antigrowth hormone, ATC Code: H01C B03

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	12/2019
4 DOSAGE AND ADMINISTRATION, 4.4 Administration	12/2019
7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic	12/2019

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SOMATULINE® AUTOGEL® [lanreotide (as acetate) injection] is indicated for:

- The long-term treatment of adult patients with acromegaly due to pituitary tumours who have had an 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 their values.
- The treatment of enteropancreatic neuroendocrine tumours in adult 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 tumours were limited (see **14 CLINICAL TRIALS, 14.2 Study Results, *Enteropancreatic NETs Study 726***).
- The treatment of adult patients with carcinoid syndrome; when used, SOMATULINE® AUTOGEL® reduces the administration frequency of short-acting somatostatin analog rescue therapy (see **14 CLINICAL TRIALS, 14.2 Study Results, *Carcinoid Syndrome Study 730***).

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in pharmacokinetics (see **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics**). It is not necessary to alter the starting dose in elderly acromegaly patients (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Acromegaly***). Clinical studies in patients with enteropancreatic neuroendocrine tumours (NETs) or carcinoid syndrome did not include sufficient numbers of patients aged 65 and over (see **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics**).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug (see **7 WARNINGS AND PRECAUTIONS, Immune**), or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTH, COMPOSITION AND PACKAGING**.
- Patients who are hypersensitive to somatostatin or related peptides.
- Patients with complicated, untreated lithiasis of the bile ducts.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Loss of blood glucose control (hypoglycemia in diabetic patients; hyperglycemia) can occur (see **7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism** and **Monitoring and Laboratory Tests**).
- Gallbladder motility may be reduced and lead to gallstone formation (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **Monitoring and Laboratory Tests**).
- Drug interaction with cyclosporine (see **9 DRUG INTERACTIONS, 9.1 Serious Drug Interactions**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Acromegaly

- After 3 months of treatment with SOMATULINE® AUTOGEL®, GH and IGF-1 levels should be measured and the dose should be adjusted based on disease progression and effectiveness of treatment (see **4.2 Recommended Dose and Dosage Adjustment**, ***Acromegaly*** and **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, *Acromegaly***).
- Slight decreases in thyroid function have been observed during treatment. Thyroid function tests are recommended where clinically indicated (see **7 WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism** and **Monitoring and Laboratory Tests, *Acromegaly***).
- Patients with moderate or severe hepatic or renal impairment should start treatment with SOMATULINE® AUTOGEL® 60 mg followed by dose adjustments. These patients have not been studied for an extended dosing interval of SOMATULINE® AUTOGEL® 120 mg (see **4.2 Recommended Dose and Dosage Adjustment, *Acromegaly***).

Acromegaly, Enteropancreatic NETs, and Carcinoid Syndrome

- Sinus bradycardia may occur in patients suffering from cardiac disorders prior to treatment initiation with SOMATULINE® AUTOGEL®, therefore, heart rate should be monitored in these patients (see **7 WARNINGS AND PRECAUTIONS, Cardiovascular** and **Monitoring and Laboratory Tests**).
- Patients treated with SOMATULINE® AUTOGEL® may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when treatment is initiated or when the dose is changed and periodically thereafter, and treatment of diabetic patients should be adjusted accordingly (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7 WARNINGS AND PRECAUTIONS**, **Endocrine and Metabolism** and **Monitoring and Laboratory Tests**).
- SOMATULINE® AUTOGEL® may reduce gallbladder motility and lead to gallstone formation. Gallbladder ultrasonography is recommended at the start of treatment and periodically thereafter. If complications of cholelithiasis are suspected, discontinue SOMATULINE® AUTOGEL® and treat appropriately (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **7 WARNINGS AND PRECAUTIONS**,

Hepatic/Biliary/Pancreatic and **Monitoring and Laboratory Tests**).

- Concomitant administration of SOMATULINE® AUTOGEL® with cyclosporin may decrease blood levels of cyclosporine, therefore, cyclosporin blood levels should be monitored (see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX** and **9 DRUG INTERACTIONS, 9.1 Serious Drug Interactions**).
- The gastrointestinal effects of SOMATULINE® AUTOGEL® may reduce the intestinal absorption of co-administered drugs. SOMATULINE® AUTOGEL® may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes. Caution should be exercised when medicinal products mainly metabolized by CYP3A4 that have a low therapeutic index are co-administered with SOMATULINE® AUTOGEL® (see **9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview**).
- Concomitant administration of bradycardia-inducing drugs may have an additive effect on the reduction of heart rate associated with SOMATULINE® AUTOGEL® treatment. Dosage adjustments of concomitant drugs may be necessary (see **9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview**).
- SOMATULINE® AUTOGEL® is not indicated for use in pediatric patients less than 18 years of age (see **1 INDICATIONS**, **1.1 Pediatrics**).
- It is not necessary to alter the starting dose in elderly acromegaly patients (see **4.2 Recommended Dose and Dosage Adjustment, *Acromegaly***). Clinical studies in patients with enteropancreatic NETs or carcinoid syndrome did not include sufficient numbers of geriatric patients aged 65 and older to recommend a dose for these patients (see **1 INDICATIONS, 1.2 Geriatrics** and **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics**).

Enteropancreatic NETs

- There is no recommended dose adjustment for mild or moderate renal impairment. There is insufficient information to recommend a dose for patients with severe renal impairment or with hepatic impairment of any severity (see **4.2 Recommended Dose and Dosage Adjustment, *Enteropancreatic NETs***).

Carcinoid Syndrome

- There is insufficient information to recommend a dose for patients with renal or hepatic impairments of any severity. Specific renal or hepatic impairment studies were not conducted in patients with carcinoid syndrome (see **4.2 Recommended Dose and Dosage Adjustment**, ***Carcinoid Syndrome***).

4.2 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 adjustments as described above (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency** and **Renal Insufficiency**).

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, Clinical Pharmacokinetics, *Pharmacokinetics of SOMATULINE® AUTOGEL® in Patients with Acromegaly***).

Health Canada has not authorized an indication for pediatric use in patients less than 18 years of age (see **1 INDICATIONS**, **1.1 Pediatrics**).

It is not necessary to alter the starting dose in geriatric patients aged 65 years and older (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions**, **Geriatrics**).

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 or upper outer thigh. Treatment with SOMATULINE® AUTOGEL® should be discontinued upon disease progression.

There is no recommended dose adjustment for mild or moderate renal impairment. There is insufficient information to recommend a dose for patients with severe renal impairment or with hepatic impairment of any severity (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency** and **Renal Insufficiency**).

Health Canada has not authorized an indication for pediatric use in patients less than 18 years of age (see **1 INDICATIONS, 1.1 Pediatrics**).

Clinical studies in patients with enteropancreatic NETs did not include sufficient numbers of

geriatric patients aged 65 and older to recommend a dose for these patients (see **1 INDICATIONS, 1.2 Geriatrics** and **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics**).

Carcinoid Syndrome
The recommended dose of SOMATULINE® AUTOGEL® is 120 mg administered every 4 weeks by deep subcutaneous injection.

If patients are already being treated with SOMATULINE® AUTOGEL® for enteropancreatic NETs, patients should not administer an additional dose for the treatment of carcinoid syndrome.

There is insufficient information to recommend a dose for patients with renal or hepatic impairments of any severity. Specific renal or hepatic impairment studies were not conducted in patients with carcinoid syndrome (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency** and **Renal Insufficiency**).

Health Canada has not authorized an indication for pediatric use in patients less than 18 years of age (see **1 INDICATIONS**, **1.1 Pediatrics**).

Clinical studies in patients with carcinoid syndrome did not include sufficient numbers of geriatric patients aged 65 and older to recommend a dose for these patients (see **1 INDICATIONS, 1.2 Geriatrics** and **7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics**).

4.3 Reconstitution

Reconstitution is not required for this drug product.

4.4 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 or in the upper outer thigh. 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.

4.5 Missed Dose

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

5 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 30 mg 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, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Deep subcutaneous injection	Injection 60 mg, 90 mg, 120 mg lanreotide (as acetate) per unit (syringe)	Glacial acetic acid, water for injection

SOMATULINE® AUTOGEL® is supplied in a sterile, pre-filled syringe (polypropylene) fitted with an automatic safety system with a plunger stopper (bromobutyl rubber) and a needle (stainless steel) covered by a plastic cap.

Each ready to use pre-filled syringe is packed in a laminated pouch (polyethylene terephtalate/aluminium/polyethylene) within a plastic tray.

Box of one individual 60 mg dose in a 0.5 mL syringe with a needle (1.2 mm X 20 mm).

Box of one individual 90 mg dose in a 0.5 mL syringe with a needle (1.2 mm X 20 mm).

Box of one individual 120 mg 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).

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

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 (see **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

In 81 patients with baseline heart rates of ≥ 60 beats per minute (bpm) treated with SOMATULINE® AUTOGEL® in enteropancreatic neuroendocrine tumours (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.

Driving and Operating Machinery

Clinical studies in patients with acromegaly, enteropancreatic NETs, or carcinoid syndrome demonstrated that adverse reactions of headache and dizziness were most commonly reported with SOMATULINE® AUTOGEL® treatment. Patients should be warned to exercise caution when driving or operating machinery while on treatment with SOMATULINE® AUTOGEL®.

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 periodically thereafter, and treatment of diabetic patients should be adjusted accordingly (see **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**). 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 (see **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Gastrointestinal

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

Hepatic/Biliary/Pancreatic

Lanreotide may reduce gallbladder motility and lead to gallstone formation. Gallbladder ultrasonography is therefore advised at the start of treatment and periodically thereafter (see **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

There have been post-marketing reports of gallstones resulting in complications, including cholecystitis, cholangitis, and pancreatitis, requiring cholecystectomy in patients taking SOMATULINE® AUTOGEL®. If complications of cholelithiasis are suspected, discontinue SOMATULINE® AUTOGEL® and treat appropriately.

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 **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency**).

Acromegaly

It is recommended that patients with moderate or severe hepatic impairment receive a starting

dose of lanreotide (as acetate) of 60 mg (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Acromegaly***).

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, Clinical Pharmacokinetics, *Pharmacokinetics of SOMATULINE® AUTOGEL® in Patients with Acromegaly***).

Enteropancreatic NETs

In patients with enteropancreatic neuroendocrine tumours, SOMATULINE® AUTOGEL® was not studied in patients with mild, moderate, or severe hepatic impairment (as per Child-Pugh score) (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Enteropancreatic NETs*** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency**).

Carcinoid Syndrome

In patients with carcinoid syndrome, SOMATULINE® AUTOGEL® was not studied in patients with mild, moderate, or severe hepatic impairment (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Carcinoid Syndrome*** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency**).

Immune

Allergic reactions (including angioedema and anaphylaxis) have been reported following the administration of SOMATULINE® AUTOGEL® (see **8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions**).

Monitoring and Laboratory Tests

Acromegaly

Evaluation of GH and IGF-1 levels are useful markers of the disease progression and effectiveness of treatment (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended dose and dosage adjustment, *Acromegaly***).

Slight decreases in thyroid function have been seen during treatment. Thyroid function tests are recommended where clinically indicated.

Acromegaly, Enteropancreatic NETs, and Carcinoid Syndrome

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. Patients treated with SOMATULINE® AUTOGEL® may experience hypoglycemia or hyperglycemia. Therefore, blood glucose levels should be monitored when lanreotide treatment is initiated or when the dosage is attuned, and periodically thereafter. The antidiabetic treatment of diabetic patients should be adjusted accordingly.

Lanreotide may reduce gallbladder motility and lead to gallstone formation. Gallbladder ultrasonography is therefore advised at the start of treatment and periodically thereafter.

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 **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency**). It is recommended that patients with moderate or severe renal impairment receive a starting dose of lanreotide of 60 mg (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Acromegaly***).

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, Clinical Pharmacokinetics, *Pharmacokinetics of SOMATULINE® AUTOGEL® in Patients with Acromegaly***).

Enteropancreatic NETs

In patients with enteropancreatic neuroendocrine tumours, no effect was observed in total clearance of lanreotide in patients with mild or moderate renal impairment receiving SOMATULINE® AUTOGEL® 120 mg. Patients with severe renal impairment were not studied (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Enteropancreatic NETs*** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency**).

Carcinoid Syndrome

In patients with carcinoid syndrome, SOMATULINE® AUTOGEL® was not studied in patients with mild, moderate, or severe renal impairment (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, *Carcinoid Syndrome*** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency**).

7.1 Special Populations

7.1.1 Pregnant Women

There is very limited experience of pregnancy in patients treated with lanreotide, either during clinical trials or from postmarketing 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 not be administered to pregnant women unless clearly needed.

7.1.2 Breast-feeding

It is unknown if the drug is excreted in human milk. SOMATULINE® AUTOGEL® should not be administered to breast-feeding women.

7.1.3 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Elderly subjects show an increase in half-life and mean residence time compared to healthy young subjects (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics**). Clinical studies conducted in patients with enteropancreatic neuroendocrine tumours or carcinoid syndrome (see **14 CLINICAL TRIALS, 14.2 Study Results, *Enteropancreatic NETs Study 726*** and ***Carcinoid Syndrome Study 730***) did not include sufficient numbers of patients aged 65 and over.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 or IGF-1 levels.

The total exposure to SOMATULINE® AUTOGEL® over the three phases of the study is summarized below.

Table 2: 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] x 28
[2] [Date of last lanreotide dose – date of first lanreotide dose] + 28

Most Commonly Reported Treatment Emergent Adverse Events (TEAEs)

The incidence of TEAEs for SOMATULINE® AUTOGEL® 60 mg, 90 mg, and 120 mg compared to placebo as investigated during the first phase of Study 717 are provided in Table 3.

Table 3: 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®				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)*
Diarrhea	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)
Anemia	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 4 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 4: 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)

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				
Diarrhea	10 (22)	19 (29)	34 (46)	50 (47)
Abdominal pain	5 (11)	8 (29)	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)
Gallbladder disorder	3 (7)	3 (5)	2 (3)	8 (7)
Bilirubinemia	1 (2)	1 (2)	0 (0)	2 (2)
Hepatomegaly	0 (0)	1 (2)	1 (1)	2 (2)
Metabolic and Nutritional Disorders				
Hyperglycemia	3 (7)	2 (3)	3 (4)	8 (7)
Weight Decrease	3 (7)	3 (5)	3 (4)	9 (8)
Hypoglycemia	1 (2)	1 (2)	0 (0)	2 (2)
Hypercholesterolemia	2 (4)	1 (2)	0 (0)	2 (2)
Phosphatase Alkaline Increased	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				
Anemia	2 (4)	2 (3)	2 (3)	6 (6)
Respiratory System Disorders				
Dyspnea	1 (2)	0 (0)	2 (3)	3 (3)
Skin and Appendages Disorders				
Alopecia	5 (11)	3 (5)	5 (7)	11 (10)
Hair disorder	1 (2)	0 (0)	2 (3)	3 (3)
Nail disorder	2 (4)	1 (2)	0 (0)	3 (3)
White Blood Cell 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.

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, edema, pain, sweating increased

Cardiovascular Disorders: cardiomegaly, ECG abnormal

Central and Peripheral Nervous System Disorders: dysesthesia, gait abnormal, hypoesthesia, paraesthesia

Endocrine Disorders: hypothyroidism

Gastrointestinal System Disorders: change in bowel habits, gastrointestinal disorder, gastroesophageal reflux, hemorrhoids, 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

Psychiatric Disorders: anxiety, appetite increased, impotence, insomnia

Reproductive Disorders: endometrial disorder

Respiratory System Disorders: bronchitis, rhinitis

Secondary Terms: cyst

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 events were 3% in the SOMATULINE® AUTOGEL® arm and 2.9% in the placebo arm.

Table 5 compares the treatment-emergent adverse events 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 5: 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)**
Diarrhea	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)
Edema peripheral	5 (5)	7 (7)
Musculo-Skeletal and Connective Tissue	**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 (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 (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 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, steatorrhea, 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 nutritional 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

Carcinoid Syndrome Study 730

The safety of SOMATULINE® AUTOGEL® 120 mg in patients with histopathologically-confirmed neuroendocrine tumours and a history of carcinoid syndrome (flushing and/or diarrhea) was evaluated in Study 730, a double-blind, placebo-controlled trial for 16 weeks, followed by open-label treatment. Patients were randomized to receive SOMATULINE® AUTOGEL® (N=59) or placebo (N=56) administered by deep subcutaneous injection once every 4 weeks. Patients in both arms of Study 730 had access to subcutaneous octreotide as rescue medication for symptom control. Patients were evaluated for safety for up to 5.4 years, with a mean duration of exposure of 2.1 years.

Adverse reactions reported in Study 730 were generally similar to those reported in Study 726 for the enteropancreatic NETs population (see **8 ADVERSE REACTIONS, Table 5** above). Treatment-emergent adverse events occurring in Study 730 in >5% of SOMATULINE® AUTOGEL®-treated patients and occurring more commonly than in placebo-treated patients (>5% higher incidence) were headache (12% vs. 5%, respectively), dizziness (7% vs. 0%, respectively), and muscle spasm (5% vs. 0%, respectively) by Week 16. Adverse reactions

occurring in Study 730 in ≥5% of SOMATULINE® AUTOGEL®-treated patients were nausea (5.2%) vs. placebo (1.8%) by Week 16.

Adverse reactions occurring at an incidence between <5% and ≥1% in the SOMATULINE® AUTOGEL® arm during the double-blind phase (by Week 16) in the Carcinoid Syndrome clinical study 730:

Blood and lymphatic system disorders*:* microcytic anemia

Ear and labyrinth disorders: deafness permanent

Gastrointestinal disorders: abdominal pain, vomiting, flatulence, constipation, abdominal pain upper, gastritis, feces pale

General disorders and administrative site conditions: fatigue, asthenia, injection site pain

Investigations: weight decreased, blood viscosity increased

Metabolism and nutritional disorders: decreased appetite, hypoglycemia

Nervous system disorders: headache, dizziness, tremor

Musculoskeletal and connective tissue disorders: myalgia

Long-term adverse reactions in Study 730:

The above-mentioned adverse reactions occurring by Week 16 persisted and were also reported during the open-label phase of Study 730. Additionally, the adverse reactions reported only during the open-label phase (with a median exposure to SOMATULINE® AUTOGEL® of approximately 20 months) but not during the 16-week double-blind phase in ≥1% of SOMATULINE® AUTOGEL®-treated patients included cholelithiasis (5.9%), abdominal distension (3.0%), hyperglycemia (3.0%), muscle spasms (2.0%), dyspepsia (2.0%), injection site induration (2.0%), and the following adverse reactions reported with an incidence of 1.0% each; diarrhea, oral pain, type 2 diabetes mellitus, neuropathy peripheral, glucose tolerance impaired, impaired fasting glucose, blood glucose increased, blood triglyceride increased, gamma-glutamyl transferase increased, edema peripheral, visceral pain, nodule, injection site erythema, injection site pruritus, arthralgia, bone pain, conjunctiva hyperaemia, tinnitus, dysmenorrhea, hot flush, confusional state, hyperhidrosis, and night sweats.

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

Acromegaly Study 717

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

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Acromegaly Study 717

Slight anemia is not uncommon in acromegaly patients. In the pivotal SOMATULINE® AUTOGEL® study no clinically meaningful changes in hematology or chemistry parameters were noted. Only small mean decreases from baseline to week 52 and last value available post-baseline were noted for all red cell parameters, including hemoglobin, 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 hematology 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.

Carcinoid Syndrome Study 730

There were no clinically relevant changes in any hematology or biochemistry parameters.

8.5 Post-Market Adverse 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 SOMATULINE® AUTOGEL® (including angioedema, anaphylaxis, and hypersensitivity) have been reported in the postmarketing environment.

Hepatobiliary disorders including cases of steatorrhea, cholecystitis, cholangitis and pancreatitis have been reported.

Occurrence of injection site abscesses at the recommended injection site have been reported.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Concomitant administration of SOMATULINE® AUTOGEL® with cyclosporin may decrease blood levels of cyclosporin (see **9.4 Drug-Drug Interactions**)

9.2 Drug Interactions 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 **DETAILED PHARMACOLOGY,**

Extrinsic Factor Pharmacokinetic Studies).

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.

Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with SOMATULINE® AUTOGEL® treatment. Dosage adjustments of concomitant drugs may be necessary.

9.3 Drug-Behavioural Interactions

Interactions with behavioural risks have not been established.

9.4 Drug-Drug Interactions

The drugs listed here 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).

Concomitant administration of SOMATULINE® AUTOGEL® injection with cyclosporin may decrease blood levels of cyclosporin, hence blood levels of cyclosporin should be monitored.

Concomitant administration of SOMATULINE® AUTOGEL® and bromocriptine increases the availability of bromocriptine.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 6: 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

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

10.2 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 lanreotide 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.

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.

10.3 Pharmacokinetics

Pharmacokinetics of SOMATULINE® AUTOGEL® in Healthy Volunteers

Table 7a: 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)	--
$t_{½}$ (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 7b: 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_{T} (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

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.

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 Vss 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.

Elimination

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 fecal excretion of unchanged lanreotide represents only a small fraction of the total dose administered.

Special Populations and Conditions

- **Pediatrics:** No studies in pediatrics were performed
- **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 Cmax of lanreotide in elderly subjects compared to healthy young subjects (see **DETAILED PHARMACOLOGY, Clinical Pharmacokinetics, *Pharmacokinetics of SOMATULINE® AUTOGEL® in Healthy Volunteers***). It is not necessary to alter the starting dose in elderly acromegaly patients.

  In a population PK analysis of enteropancreatic 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.
- **Sex:** No gender differences were found in PK parameters.
- **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***).

  No enteropancreatic NETs or carcinoid syndrome 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 moderate 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***).

No effect on clearance of lanreotide was observed in a population PK analysis of enteropancreatic NETs patients, including 165 patients with mild or moderate renal impairment (106 and 59, respectively) treated with SOMATULINE® AUTOGEL®. Enteropancreatic NETs patients with severe renal impairment were not studied. In patients with carcinoid syndrome, SOMATULINE® AUTOGEL® was not studied in patients with mild, moderate, or severe renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store under refrigeration (+2 to +8°C) in its original package in order to protect from light. Do not freeze.

Leave at room temperature for 30 minutes before administration.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

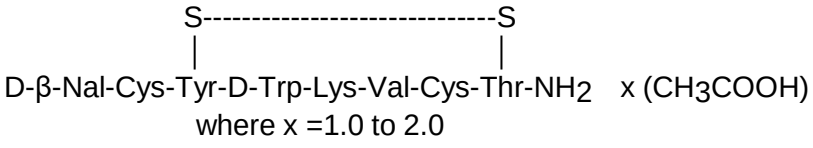
Drug Substance

Proper name: Lanreotide acetate (USAN)

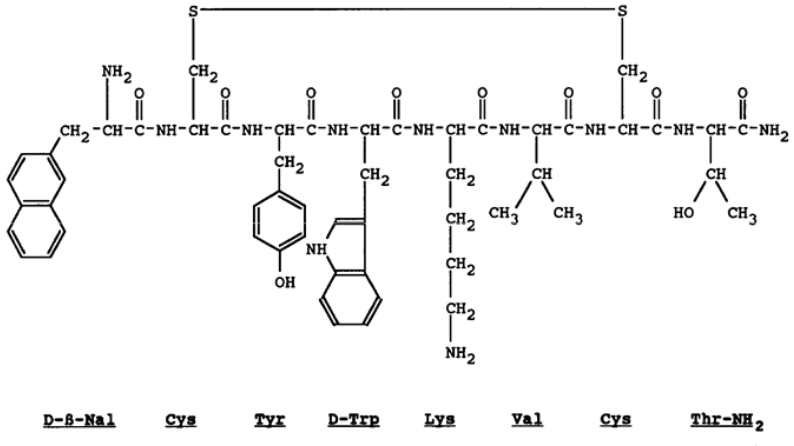
Chemical name: [cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide, acetate

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

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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 8: Summary of patient demographics for clinical trials

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
E-28-52030-717	Randomized, double blind, placebo-controlled study	SOMATULINE® AUTOGEL® (60, 90 or 120 mg), injection Placebo, injection	N=108	54 (19, 84)	47%M
2-55-52030-726	Fixed-duration, randomized, double-blind, multicenter, placebo-controlled study	SOMATULINE® AUTOGEL® (120 mg), injection Placebo, injection	N=101 N=103	63 (30,83) 62 (31,92)	53%M 52%M
2-55-52030-730	Multicenter, randomized, 16-week, double-blind, placebo-controlled trial	SOMATULINE® AUTOGEL® (120 mg), injection Placebo, injection	N=59 N=56	57.9 (38,77) 59.3 (27,85)	46%M 38%M

A brief description with more details of study design, route of administration, duration of treatment, demographic characteristics of study population, and baseline disease characteristics is described below for each study per indication followed by the study results for each study.

14.2 Study Results

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 subcutaneous (s.c.) injection of SOMATULINE® AUTOGEL® 60 mg, 90 mg, 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.

Table 9: Results of Acromegaly Study 717

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 tumours 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%) tumours, 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 Tumours (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 demographics and disease characteristics are summarized in Table 10.

Table 10: Summary of Baseline Patient Demographics and Disease Characteristics ~~in~~ for Study 726 in 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 tumour 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[a]	18 (17.8)	23 (22.3)
Grade of tumour[b], n (%)		
G1	69 (68.3)	72 (69.9)
G2	32 (31.7)	29 (28.2)
Missing	0	2 (1.9)
Hepatic tumour 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	86 (86.1)	88 (85.4)
Previous surgery of the primary tumour, 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 Missing	66 (65.4) 2 (2.0)	66 (64.1) 3 (2.9)
Progression at baseline, n (%) Yes No	 4 (4.0) 97 (96.0)	 5 (4.9) 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
[a]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)
[b]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%

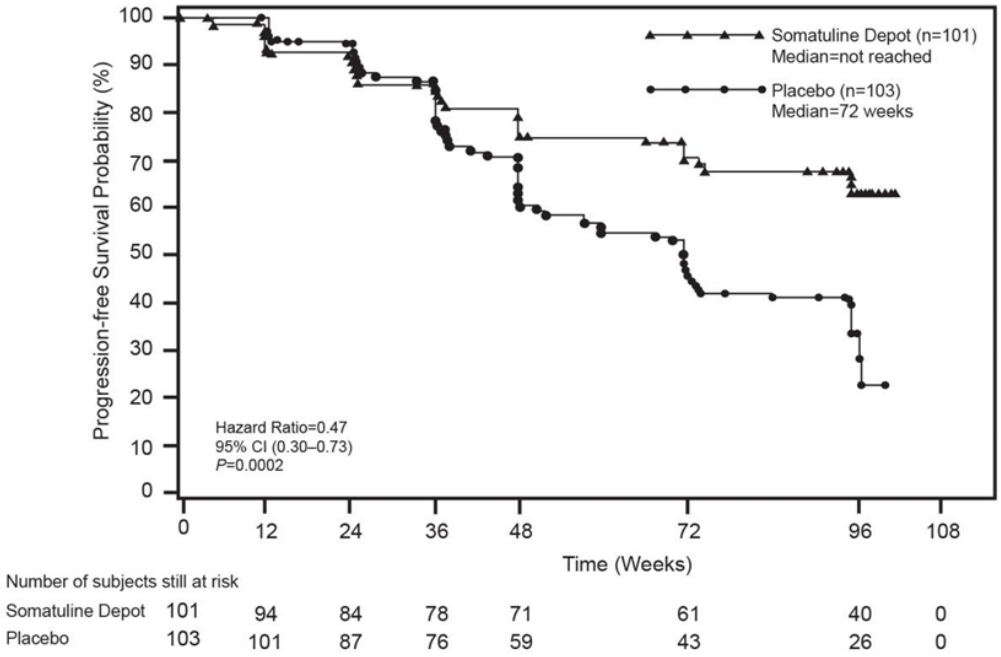
Monthly treatment with SOMATULINE® AUTOGEL® demonstrated a statistically significant improvement in PFS, resulting in a 53% reduction in tumour progression or death when compared to placebo (p=0.0002). The median PFS for SOMATULINE® AUTOGEL® was not reached at 96 weeks while the median PFS for placebo was 72 weeks, as shown in Table 11 and Figure 1.

Table 11: Results of Study 726 in patients with Enteropancreatic NETs

	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

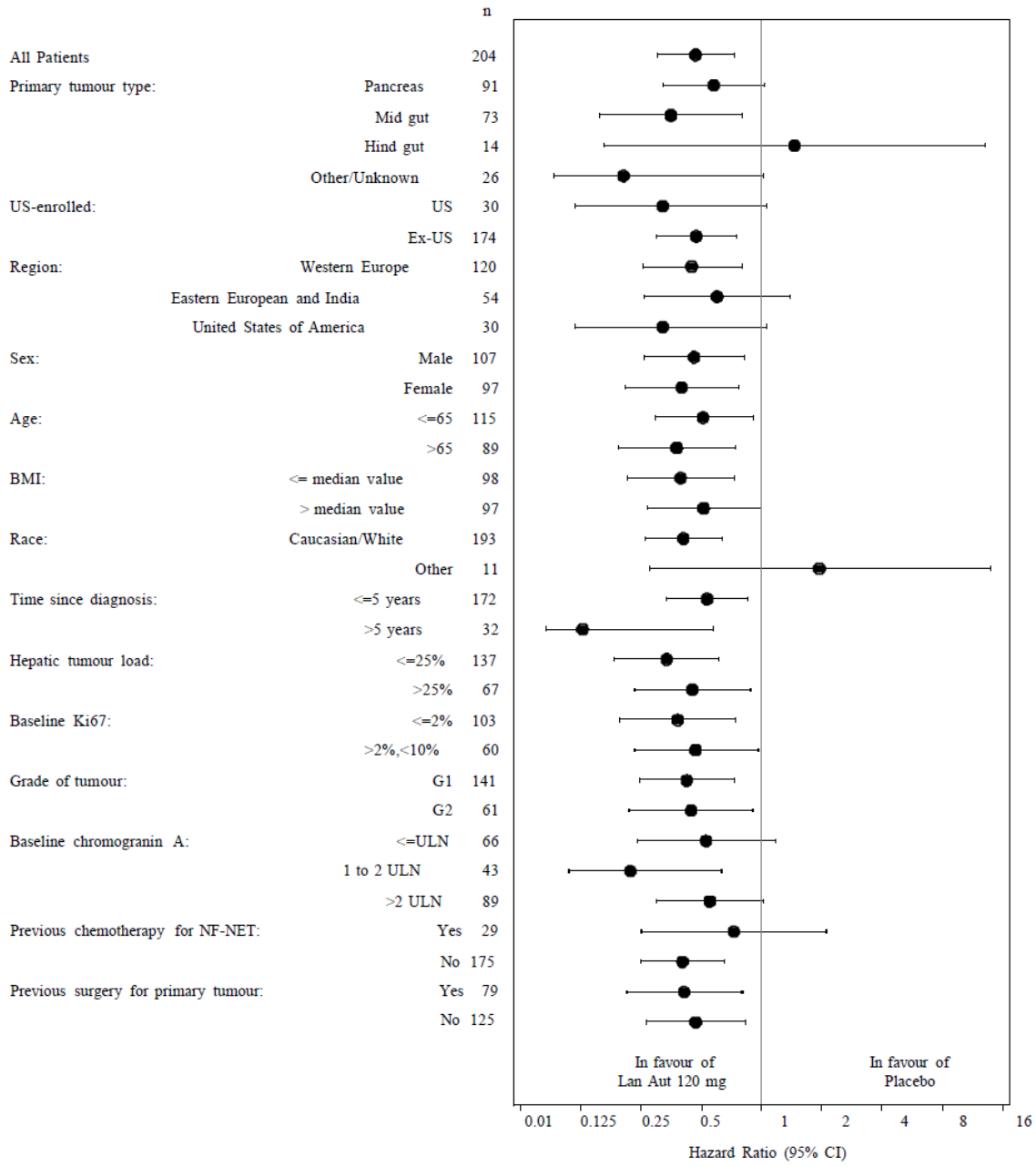
NC= not calculable

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 tumour, hepatic tumour load, previous chemotherapy, baseline Ki67, tumour 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

Carcinoid Syndrome Study 730

Study 730 was a multicenter, randomized, 16-week, double-blind, placebo-controlled trial of 115 patients with histopathologically-confirmed neuroendocrine tumours and a history of carcinoid syndrome (flushing and/or diarrhea). The study duration for efficacy was 52 weeks (4 weeks baseline screening, 16 weeks double-blind treatment, and 32 weeks open-label treatment), followed by an extended open-label safety phase.

Patients were randomized 1:1 to receive SOMATULINE® AUTOGEL® 120 mg (n=59) or placebo (n=56) by deep subcutaneous injection every 4 weeks. Patients were instructed to self-administer a short acting somatostatin analog (SSA) (subcutaneous octreotide ≤600µg per day) as rescue medication, as needed, for symptom control. The use of short-acting octreotide and the severity and frequency of diarrhea and flushing symptoms were reported daily in electronic patient diaries. The primary efficacy outcome measure was the percentage of days in which patients received at least one injection of rescue medication for symptom control during the 16-week double-blind phase. Average daily frequencies of diarrhea and flushing events were assessed secondarily.

The patient population had a mean age of 58.6 years (range 27-85 years), 58% were female and 77% were Caucasian. The study included patients who had been previously treated with a SSA, as well as patients who were SSA-naïve. Fifty six percent of patients had received SSA therapy (octreotide) prior to randomization (see Table 12), and 84% of patients experienced moderate or severe diarrhea or flushing at baseline.

Table 12: Baseline Clinical and Demographic Characteristics in Study 730

	Somatuline® Autogel® 120 mg (N=59)	**Placebo (N=56)**
Age (years)		
Mean	57.9	59.3
Sex, n (%)		
Male	27 (45.8)	21 (37.6)
Female	32 (54.2)	35 (62.5)
Race, n (%)		
White	44 (74.6)	44 (78.6)
Multiracial	7 (11.9)	6 (10.7)
Asian	6 (10.2)	3 (5.4)
Black/African American	2 (3.4)	3 (5.4)
Time from first symptom to study treatment initiation, n (%)		
<1 year	14 (23.7)	18 (32.1)
≥1 year	45 (76.3)	38 (67.9)
Time from diagnosis to study treatment initiation, n (%)		
<1 year	19 (32.2)	22 (39.3)
≥1 year	40 (67.8)	34 (60.7)
Region and prior SSA therapy, n (%)		
United States	21 (35.6)	19 (33.9)
Prior SSA therapy	19 (32.2)	17 (30.4)
SSA-naive	2 (3.4)	2 (3.6)
Non-United States	38 (64.4)	37 (66.1)
Prior SSA therapy	14 (23.7)	14 (25)
SSA-naive	24 (40.7)	23 (41.1)
Prior SSA therapy ≤3 months before screening, n (%)		
Yes	28 (47.5)	28 (50)
No	31 (52.5)	28 (50)
Prior use of short-acting octreotide, n (%)		
Yes	15 (25.4)	9 (16.1)
No	44 (74.6)	47 (83.9)
Use of short-acting octreotide during screening, n (%)		

Yes	30 (50.8)	29 (51.8)
No	29 (49.2)	27 (48.2)

Patients in the SOMATULINE® AUTOGEL® arm had 15% fewer days on rescue medication compared to patients in the placebo arm (33.7% vs 48.5% of days, respectively; p=0.0165). The beneficial effect of SOMATULINE® AUTOGEL® in reducing rescue medication use was evident regardless of baseline characteristics, including prior SSA use, duration of prior SSA use, and global region.

The average daily frequencies of diarrhea and flushing events in patients treated with SOMATULINE® AUTOGEL® (and rescue medication) were numerically lower compared to patients treated with placebo (and rescue medication), but were not statistically significantly different by hierarchical statistical testing.

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 normalization at these concentrations). Non-responders do not respond to lanreotide treatment even with high lanreotide concentrations.

In Study 730, patients with carcinoid syndrome treated with SOMATULINE® AUTOGEL® 120 mg every 4 weeks showed greater reduction from baseline to Week 12 in mean levels of urinary 5-hydroxyindole acetic acid (5-HIAA) compared with placebo.

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. Similar 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. In Study 730, less than 2% (2 of 108) of carcinoid syndrome patients treated with SOMATULINE® AUTOGEL® developed anti-lanreotide antibodies.

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.

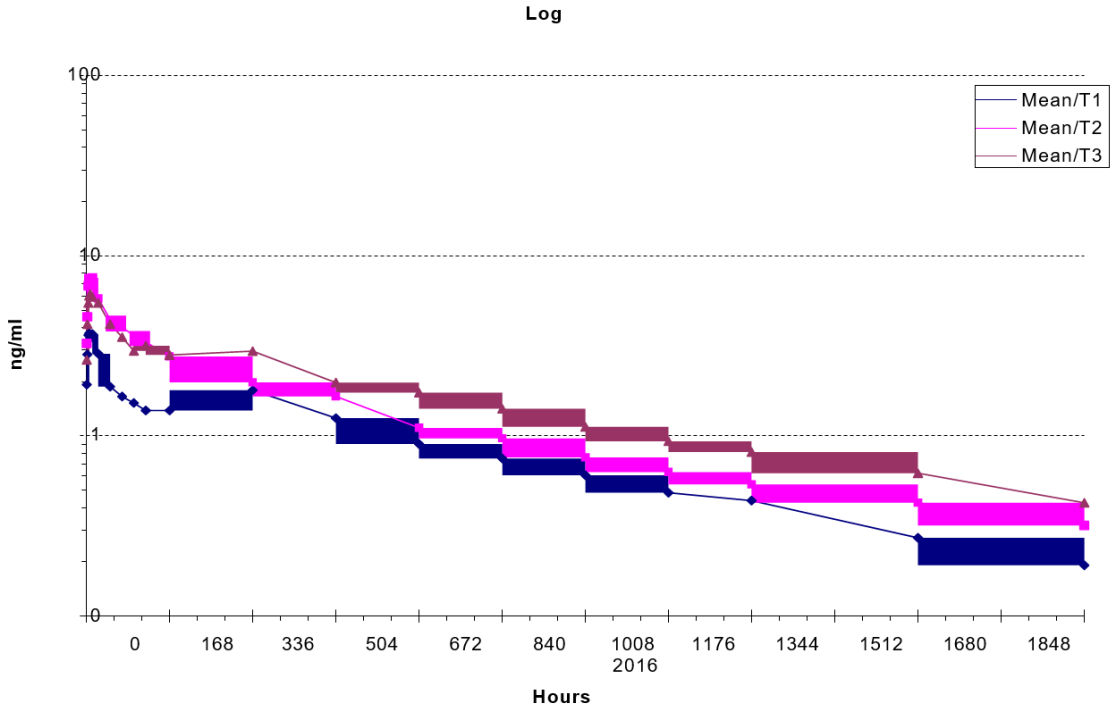
Clinical Pharmacokinetics

Pharmacokinetics of SOMATULINE® AUTOGEL® in Healthy Volunteers

Descriptive pharmacokinetics 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 s.c. 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 s.c. 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 s.c. administration of SOMATULINE® AUTOGEL® to healthy volunteers are summarized below.

Table 13: Pharmacokinetic parameters following a single deep subcutaneous administration of SOMATULINE® AUTOGEL® 60, 90, and 120mg to healthy volunteers

Parameter	60mg (N=13)			90mg (N=13)			120mg (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
$t_{½}$ (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 90mg but at 120mg 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 $t_{½}$, t_{lag}, MRT (Mean Residence Time), MAT (Mean Absorption Time) and F% showed similar values in the three dose groups. Mean $t_{½}$ 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 randomized parallel-group, double-blind, single-center study that evaluated the pharmacokinetic profile of SOMATULINE® AUTOGEL® administered at fixed doses of 60, 90, and 120mg 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 120mg. Dose proportionality was observed in the pharmacokinetic parameters $C_{min,\,1}$, C_{max}, and AUC_T as shown in the table below.

Table 14: Comparative Mean (± SD) Pharmacokinetic Parameters Following a First Single Dose of SOMATULINE® AUTOGEL® of 60, 90, and 120mg to Patients with Acromegaly

Parameter (units)	60mg			90mg			120mg			p
	Mean	SD	N	Mean	SD	N	Mean	SD	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} ($ng.mL^{-1}$)	0.725	0.191	6	0.973	0.199	5	1.406	0.306	6	0.699[(2)]
AUC_t ($ng.mL^{-1}$ 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 14). Pharmacokinetic parameters $C_{min.ss}$, $C_{max\,ss}$, and AUC 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 120mg dose levels, respectively.

Table 15: Comparative Mean (± SD) Steady-State Pharmacokinetic Parameters Following Four Doses of SOMATULINE® AUTOGEL® 60, 90, 120 mg to Patients with Acromegaly

Parameter (units)	60mg			90mg			120mg			p
	Mean	SD	N	Mean	SD	N	Mean	SD	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)]
$C_{max.ss}$	3.821	0.509	4	5.694	1.672	6	3.053	0.932	6	0.974[(2)]

($ng.mL^{-1}$)										
$C_{min.ss}$ ($ng.mL^{-1}$)	1.822	0.304	4	2.511	0.882	6	3.762	1.012	6	0.721[(2)]
AUC_t ($ng.mL^{-1}$ d)	68.79	8.53	4	85.11	17.10	6	4.523	0.988	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 120mg, with values of 81%, 108%, and 86% for the 60, 90, and 120mg 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, and 120mg 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 120mg and the 60mg 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 120mg 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 120mg). Consistent observations were made after multiple deep s.c. injections.

Pharmacokinetic data from studies evaluating the use of extended dosing intervals of SOMATULINE® AUTOGEL® 120mg 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 ≤ 2.5ng/mL ranged from 0,95 to 1.13 ng/mL.

Studies evaluating the use of extended dosing intervals of SOMATULINE® AUTOGEL® 120mg 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 16.

Table 16: Summary Statistics of Lanreotide Pool PK Model Parameters

	CL/F (L/day) [a]	V/F (L)	K_A (day^{-1})	$t_{½}K_A$ (days)
Somatuline Autogel 120mg (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 17 and for steady state in Table 18.

Table 17: Summary Statistics of Derived SOMATULINE® AUTOGEL® 120mg 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 18: Summary Statistics of Derived SOMATULINE® AUTOGEL® 120mg 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); SD = standard deviation

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® 120mg 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 s.c. 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 s.c. 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 metabolized 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 19: 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.

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 pharmacodynamics 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

An immediate-release formulation (IRF) of lanreotide, administered either by s.c. injection or as an intravenous (i.v.) 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 20: 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, 180mg/kg	<30	30	120-135
Rat	i.v.	3, 6, 24, 48, 60, 75mg/kg	3	>6	>48
Mouse	s.c.	0.8, 600, 900, 1200mg/kg	<600	600	>1200
Rat	s.c.	0.8, 1500mg/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.

Table 21: 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 (i.m.) and intravenous administrations were assessed in mice and/or rats and dogs (see Table 21). 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 22: 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.

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 human, 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.

Genotoxicity

Table 23: 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 was performed. In this set of studies, no positive results were obtained.

Reproductive and Developmental Toxicology

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 24: 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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrSOMATULINE® AUTOGEL®

Lanreotide Injection

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

Read this carefully before you start taking **SOMATULINE® AUTOGEL®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SOMATULINE® AUTOGEL®**.

Serious Warnings and Precautions

Treatment with SOMATULINE® AUTOGEL® may:

- cause loss of blood sugar control if you have diabetes. Diabetes is a disease in which your blood sugar levels are too high.
- cause gallstones in your gallbladder.
- affect how well a drug called cyclosporine works. Cyclosporine is used to reduce the activity of the immune system. Taking SOMATULINE® AUTOGEL® may lower the levels of cyclosporine in your blood.

What is SOMATULINE® AUTOGEL® used for?

SOMATULINE® AUTOGEL® is recommended for:

- The treatment of adults with acromegaly. Acromegaly is a condition where a gland in your brain produces too much growth hormone.
- The treatment of adults with a type of cancer known as enteropancreatic neuroendocrine tumours. Enteropancreatic neuroendocrine tumours begin to grow in the stomach, intestines, appendix, or the pancreas. SOMATULINE® AUTOGEL® treats and controls the growth of tumours of the intestine and pancreas that:
    - cannot be removed by surgery or;
    - have spread
- The treatment of adults with carcinoid syndrome. Carcinoid syndrome is a cancer condition that makes and releases certain chemicals into your blood. SOMATULINE® AUTOGEL® reduces the need for rescue drugs to treat carcinoid syndrome.

SOMATULINE® AUTOGEL® is not for use in children and adolescents under the age of 18.

How does SOMATULINE® AUTOGEL® work?

Lanreotide, the medicinal ingredient in SOMATULINE® AUTOGEL®, belongs to a group of medicines called antigrowth hormones. Lanreotide is similar to a hormone naturally made in your body called somatostatin. SOMATULINE® AUTOGEL® is believed to lower the levels of hormones in the body such as GH (growth hormone) and IGF-1 (insulin-like growth factor-1) and blocks the release of some hormones and secretions in the stomach and intestines.

Additionally, it has an effect on some type of tumours of the intestine and pancreas by stopping or delaying their growth.

What are the ingredients in SOMATULINE® AUTOGEL®?

Medicinal ingredients: lanreotide acetate.

Non-medicinal ingredients: glacial acetic acid and water for injection.

SOMATULINE® AUTOGEL® comes in the following dosage forms:

Solution for injection: 60 mg, 90 mg, 120 mg lanreotide (as acetate).

Do not use SOMATULINE® AUTOGEL® if you:

- are allergic to lanreotide or any of the other ingredients of SOMATULINE® AUTOGEL®.
- are allergic to somatostatin or any other drug similar to somatostatin.
- have untreated gallstones.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SOMATULINE® AUTOGEL®. Talk about any health conditions or problems you may have, including if you:

- are **diabetic**. Treatment may affect your blood sugar levels. Your doctor may monitor your blood sugar levels after your first dose, when your dose is changed, and every so often during your treatment. The doctor may also alter the drugs you use to treat your diabetes.
- have or have had **liver problems**.
- have or have had **kidney problems**.
- have or have had **heart problems**. Treatment may slow your heart rate. Your doctor may monitor your heart rate while on treatment.
- have or have had **gallbladder problems**. Treatment may lead to the formation of gallstones in your gallbladder. Your doctor may monitor your gallbladder when you take your first dose and while on treatment. Treatment may end should complications of gallstones occur.
- have **thyroid problems**. Treatment may decease your thyroid function if you are being treated for acromegaly.
- are **pregnant, planning to become pregnant**. Avoid becoming pregnant while you are taking SOMATULINE® AUTOGEL®.
- are **breast-feeding**.

Other warnings you should know about:

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to SOMATULINE® AUTOGEL®. Dizziness and headaches can occur after the first dose and when the dose is increased.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SOMATULINE® AUTOGEL®:

- Cyclosporine, which is a drug that blocks the activity of the immune system.
- Bromocriptine, which is a drug that blocks prolactin (a hormone released by the pituitary gland).
- Bradycardia inducing drugs, which are drugs that slow heart rate (e.g., beta-blockers).

How to take SOMATULINE® AUTOGEL®:

- Take SOMATULINE® AUTOGEL® exactly as your doctor has told you. Speak to your doctor or pharmacist if you are not sure.
- SOMATULINE® AUTOGEL® is given as a deep subcutaneous (under the skin) injection into the buttock or the upper outer thigh.
- SOMATULINE® AUTOGEL® is given by a healthcare professional or a properly trained person.
- You may give yourself an injection, in the thigh region only. You should be properly trained and be able to follow the Instructions for Use of SOMATULINE® AUTOGEL®

Usual Adult Dose:

Treatment for Acromegaly

The recommended starting dose is one injection of SOMATULINE® AUTOGEL® 90 mg every 28 days. If you have liver or kidney problems, the recommended starting dose is one injection of SOMATULINE® AUTOGEL® 60 mg every 28 days.

Your doctor:

- May change the dose or the length of time between your injections. This depends on how your symptoms and hormones respond to the treatment and whether you have liver or kidney problems.
- Will tell you how long you need to receive SOMATULINE® AUTOGEL®.

Treatment for Enteropancreatic Neuroendocrine Tumours or Carcinoid Syndrome

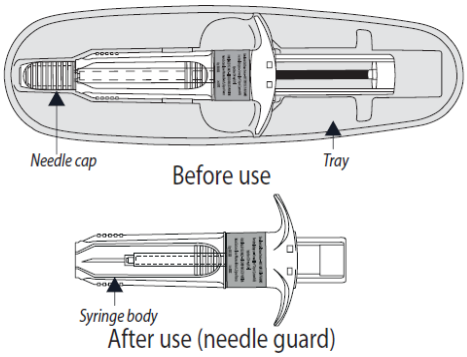
The recommended dose is one injection of SOMATULINE® AUTOGEL® 120 mg every 28 days. Your doctor may change your dose if you have liver or kidney problems. Your doctor will tell you how long you need to receive SOMATULINE® AUTOGEL®.

If you are already being treated for enteropancreatic neuroendocrine tumours, you do not need to take an extra dose of SOMATULINE® AUTOGEL® for the treatment of carcinoid syndrome.

Instructions for Use

Attention: Read all the instructions carefully before starting the injection. This specific technique must be followed to give the dose. The following instructions explain how to inject SOMATULINE® AUTOGEL®.

SOMATULINE® AUTOGEL® is supplied in a ready to use pre-filled syringe. It is fitted with an automatic safety system where the needle will be pulled inside after the full dose is given. This is to prevent needle stick injury.



1. Remove SOMATULINE® AUTOGEL® from the fridge 30 minutes before the injection. Injecting cold medication may be painful. Keep laminated pouch sealed until just prior to injection.

2. Before opening the pouch, check that the pouch is intact and that the medication has not expired.

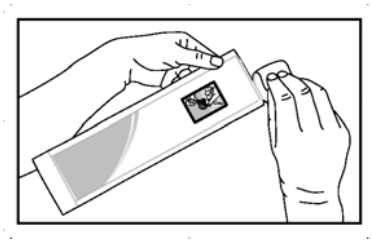
Do not use the pre-filled syringe:

- If you drop or damage it, or
- If the pre-filled syringe or pouch appears damaged in any way, or
- If the product has expired. The expiry date is printed on the outer carton and the pouch.

If any of the above apply, contact your doctor or pharmacist.

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

4. Tear-open the pouch along the dotted line. Take out the pre-filled syringe.



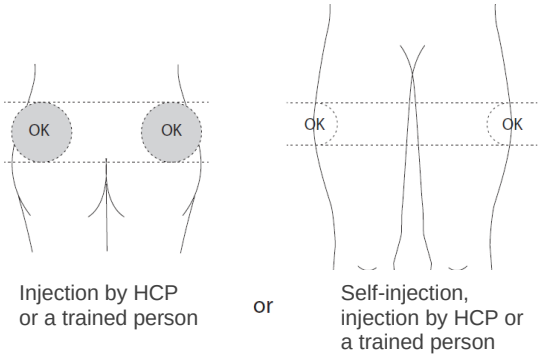
5. Prior to administration, look closely at the SOMATULINE® AUTOGEL® syringe. Check for particles and discolouration. The content of the prefilled syringe has a gel-like appearance. It will be white to pale yellow in colour. Do not administer if you see particles or if there is a change in colour. The solution can also contain bubbles that can clear up during injection. This is normal.

6. Select an injection site. Avoid areas with moles, scar tissue, reddened skin, or skin that feels bumpy. Be sure to switch between (alternate) the right and left side each time an injection is given. The location of the injection site is based on who is giving the injection. If the injection is given by:

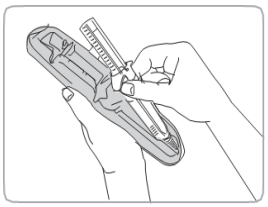
6a: a healthcare professional (HCP) or someone else like a trained family member or friend: The upper external quadrant of the buttock or upper outer thigh, or

6b: yourself: The upper outer part of your thigh

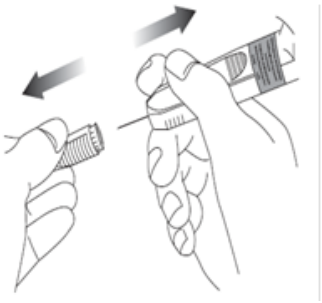
6a (Upper external quadrant of buttock) 6b (upper outer thigh)



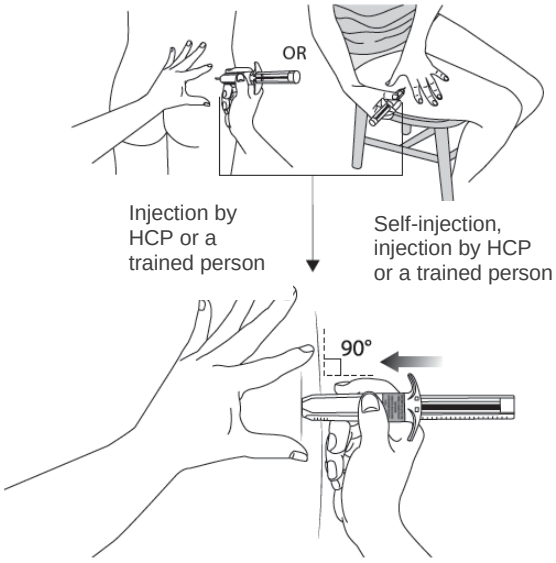
7. Clean the injection site with a sterile gauze without rubbing the skin too much.
8. Before injecting, take the pre-filled syringe out of its tray. Discard the tray.



9. Remove the needle cap by pulling off and discard it.



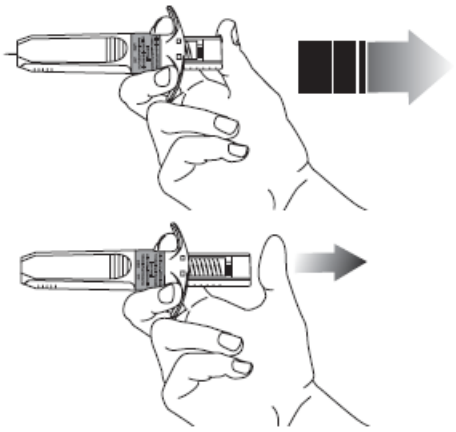
10. Use your thumb and index finger (of the hand not holding the syringe) to stretch and flatten the skin. Do not pinch, fold, or press on the skin at the injection site. Use a strong, straight, dart-like motion to quickly insert the needle. Be sure to insert the needle perpendicular (90 degree angle) to and all the way into your skin. It is very important that you insert the needle completely. You should not see any needle once it is inserted all the way into your skin.



11. Let go of the injection site area that has been flattened by your hand. Using your other hand, push the plunger with steady and very firm pressure. The medication is thicker and harder to push than you might expect. **Typically 20 seconds are needed**. Inject the full dose and give a final push to make sure you cannot push it any further. Keep your thumb on the plunger to stop the automatic safety system from being activated too soon.

12. Without releasing the pressure on the plunger, pull the needle from out of your skin.

13. Take your thumb off the plunger, to release pressure on the plunger. The needle will be automatically pulled into the needle guard where it will be locked permanently.



14. Use a dry cotton ball or sterile gauze and apply gentle pressure to the injection site. This will help to prevent any bleeding. **Do NOT rub or massage the injection site after the injection.**

15. Properly dispose of the used syringe.

Overdose:

If you think you, or a person you are caring for, have taken too much SOMATULINE® AUTOGEL®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

As soon as you realize 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.

What are possible side effects from using SOMATULINE® AUTOGEL®?

These are not all the possible side effects you may have when taking SOMATULINE® AUTOGEL®. If you experience any side effects not listed here, tell your healthcare professional.

- Cold-like symptoms (cough, runny nose, sore throat, fever)
- Confusion
- Constipation
- Dizziness
- Dry mouth
- Excessive sweating, night sweats
- Fatty stools (stools may be bulky and appear pale and oily)
- Feeling hot with reddening of the skin
- Flatulence (passing gas)
- Hair loss
- Hard swelling of the injection site, and rarely a persistent hard swelling

- Heartburn
- Indigestion
- Joint, bone, or mouth pain
- Loss of appetite
- Muscle pains or spasms
- Nausea
- Pain during menstruation
- Ringing in the ears
- Shaking
- Swelling in the arms
- Swollen tummy
- Weakness, numbness, tingling or pain in the hands, feet, or back
- Weight loss

SOMATULINE® AUTOGEL® can cause abnormal blood test results. Your doctor will decide when to perform blood tests and other tests like gall bladder ultrasound. Your doctor will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Abdominal pain	X		
Diarrhea or loose stools	X		
Formation of gallstones in the gall bladder: sudden severe pain in the upper right abdomen which may last for hours, maybe accompanied by nausea and vomiting		X	
Headache	X		
Vomiting	X		
Anemia (decreased number of red blood cells): fatigue, loss of energy, weakness, shortness of breath	X		
COMMON			
Injection site reaction: site of injection may be tender, warm, swollen, red or itchy with a build-up of pus under the skin	X		
Decreased heart rate (bradycardia)		X	
Eye problems: clouding of the lens in the eye, blurry vision, eye redness, dim vision, and/or eye pain		X	
Heart Disorders (disorders affecting your heart muscle, valves or rhythm): Chest pain, or chest discomfort, high blood pressure, irregular heart rhythm, shortness		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
of breath, fainting, swelling of the legs, ankles and feet, weakness			
High blood pressure or worsening of high blood pressure: headaches, nausea and vomiting		X	
Underactive thyroid gland (hypothyroidism): changes in heart rate, appetite or weight, tiredness, feeling cold or swelling at the front of the neck		X	
Pancreatitis (inflammation of the pancreas): severe abdominal pain which may spread out towards the back, nausea, vomiting, increased heart rate		X	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, itching, bruising, weight loss		X	
Diabetes, worsening of diabetes, or high blood sugar: unusual thirst, frequent urination, extreme fatigue or lack of energy, tingling or numbness in the hands or feet		X	
Low blood sugar: dizziness, sweating, confusion, headache, blurred vision, fast heartbeat, mood changes		X	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine	X		
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of anxiety, worthlessness, guilt, regret, helplessness, hopelessness or reduced libido (sex drive)	X		
New Tumour growth		X	
Deafness: loss of hearing		X	
RARE			
Allergic skin reactions: rash, hives, itching, redness	X		
UNKNOWN			
Severe allergic reactions: swollen face, lips, mouth or tongue,		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
tightness in chest, shortness of breath or wheezing fainting, dizziness or feeling lightheaded due to a drop in blood pressure, flushing or redness of the skin, rash or hives			
Inflammation of the bile duct: pain in the upper right part of your belly (abdomen), fever, chills, yellowing of the skin and eyes (jaundice), nausea, vomiting, clay-coloured stools, dark urine, tiredness		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store SOMATULINE® AUTOGEL® at 2ºC-8ºC in a refrigerator in its original package in order to protect from light. 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. Each syringe is packed individually.

Keep out of reach and sight of children.

If you want more information about SOMATULINE® AUTOGEL®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.ipsen.ca, or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharmaceuticals Canada Inc.

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