

New Zealand Datasheet

1. PRODUCT NAME

SOMATULINE AUTOGEL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lanreotide acetate 60, 90 and 120 mg solution for Injection in a pre-filled syringe.

3. PHARMACEUTICAL FORM

Lanreotide (presented as lanreotide acetate 60 mg, 90 mg, 120 mg) solution for injection in a pre-filled syringe. White to pale-yellow semi-solid formulation. Somatuline Autogel is formulated as a prolonged-release solution of lanreotide acetate for deep subcutaneous injection. Prolonged release of the peptide is achieved by the physical nature of the supersaturated solution.

Each pre-filled syringe contains a supersaturated solution of lanreotide acetate corresponding to 24.6 mg of lanreotide base per 100 mg of solution, which ensures an actual injection dose of 60 mg, 90 mg and 120 mg of lanreotide, respectively.

The formulation contains water for injections and glacial acetic acid (for pH adjustment) as excipients. The pH of Somatuline Autogel solution is around 6.1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Somatuline Autogel is indicated for:

- the treatment of acromegaly when the circulating levels of growth hormone and IGF-1 remain abnormal after surgery and/or radiotherapy or in patients who are dopamine agonist treatment refractory
- the treatment of symptoms of carcinoid syndrome associated with carcinoid tumours
- the treatment of well or moderately differentiated gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adult patients with unresectable locally advanced or metastatic disease.

4.2 Dosage and method of administration

Posology:

Acromegaly:

In patients receiving a somatostatin analogue for the first time, the recommended starting dose is 60 mg of Somatuline Autogel administered every 28 days.

In patients previously treated with Somatuline LA once every 14 days, the initial dose of Somatuline Autogel should be 60 mg every 28 days; in patients previously treated with Somatuline LA once every 10 days, the initial dose of Somatuline Autogel should be 90 mg every 28 days, and in patients treated with Somatuline LA once every 7 days, the initial dose of Somatuline Autogel should be 120 mg every 28 days.

Thereafter, in all patients, the dosage strength (60 mg, 90 mg and 120 mg) should be individualised according to the response to treatment (as judged by a reduction in GH and/or IGF-1 levels).

If the desired response is not obtained, the dose may be increased.

If complete control is obtained (based on GH levels under 1 µg/L, normalised IGF-1 levels and/or disappearance of symptoms), the dose may be decreased.

Patients well controlled on lanreotide can be treated with Somatuline Autogel 120 mg every 42-56 days.

Long term monitoring of symptoms, GH and IGF-1 levels should be undertaken as clinically indicated.

Symptoms of Carcinoid Syndrome:

The recommended starting dose is 60 to 120 mg administered every 28 days. The dose should be adjusted according to the degree of symptomatic relief obtained.

Treatment of gastroenteropancreatic neuroendocrine tumours in adult patients with unresectable locally advanced or metastatic disease:

The recommended dose of Somatuline Autogel is one injection of 120 mg administered every 28 days. The treatment with Somatuline Autogel should be continued for as long as needed for tumour control.

Use in renal or hepatic impairment

Subjects with severe renal impairment show an approximately two-fold decrease in total serum clearance of lanreotide, with a consequent increase in half-life and AUC. In subjects with moderate to severe hepatic impairment a reduction in clearance (30%) and an increase in volume of distribution and mean residence time are observed.

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

No GEP-NET patients with hepatic impairment (as per Child-Pugh score) were studied.

In patients with hepatic/renal dysfunction, kidney and liver function should be regularly monitored. Due to the wide therapeutic window of lanreotide, it is not necessary to adjust the dose in these circumstances.

Method of administration

Somatuline Autogel should be injected via the deep subcutaneous route in the superior external quadrant of the buttock by a healthcare professional. The deep subcutaneous injection should be given at varying places in the buttock or upper outer thigh.

For patients who are controlled on Somatuline Autogel, the product may be administered either by the patient or their carer, who both must be motivated and competent to perform the injection following appropriate training. In the case of self-injection, the injection should be given in the upper outer thigh.

The decision regarding administration of Somatuline Autogel by the trained patient / carer should be taken by a health professional. A monitoring system should be in place for such patients to ensure the maintenance of their disease control in the long term.

Regardless of the site of injection, the skin should not be folded and 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 side.

Pharmaceutical Precautions

Do not use if the laminated pouch is damaged or opened.

Instructions for use/handling

The solution for injection in a pre-filled syringe is ready for use.

After opening the protective laminated pouch, the product should be administered immediately.

For use in one patient on one occasion only. Discard any residue. Contains no antimicrobial preservative.

NB: It is important that injection of this product is performed according to the instructions in the package leaflet.

4.3 Contraindications

Somatuline Autogel should not be prescribed during lactation, nor in patients presenting with hypersensitivity to the peptide or related peptides or any of the excipients.

4.4 Special warnings and precautions for use

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and its analogues inhibit secretion of insulin and glucagon. Hence, patients treated with Somatuline Autogel may experience hypoglycaemia or hyperglycaemia. Blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose is altered, and treatment of diabetic patients should be accordingly adjusted. 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.

Lanreotide may reduce gall bladder motility and therefore, gall bladder echography is advised at the start of treatment and every six months thereafter. There have been postmarketing reports of gallstones resulting in complications, including cholecystitis, cholangitis, and pancreatitis, requiring cholecystectomy in patients taking lanreotide. If complications of cholelithiasis are suspected, discontinue lanreotide and treat appropriately.

In patients with hepatic/renal dysfunction, kidney and liver function should be regularly monitored (see 'Use in Renal or Hepatic Impairment').

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. Care should be taken when initiating treatment with lanreotide in patients with bradycardia.

In 81 patients with baseline heart rates of ≥ 60 beats per minute (bpm) treated with Somatuline Autogel in Study 726 in GEP NET patients, 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.

Paediatric Use

As there is no experience of the use of the product in children, the use of Somatuline Autogel in children cannot be advised.

Use in the elderly

Elderly subjects show an increase in half-life and mean residence time compared with healthy young subjects. Due to the wide therapeutic window of lanreotide, it is not necessary to adjust

the dose in these circumstances.

In a population PK analysis of GEP-NET patients including 122 patients aged 65 to 85 years, no effect of age on clearance and volume of distribution of lanreotide was observed.

4.5 Interaction with other medicines and other forms of interaction

The gastrointestinal effects of Somatuline Autogel may result in the reduction of the intestinal absorption of co-administered drugs. As with other somatostatin analogues, Somatuline Autogel may reduce the intestinal absorption of cyclosporin A.

Concomitant administration of cyclosporine with lanreotide may decrease the relative bioavailability of cyclosporine and therefore may necessitate the adjustment of cyclosporine dose to maintain therapeutic levels.

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

Limited published data indicate that concomitant administration of somatostatin analogues and bromocriptine may increase the availability of bromocriptine.

Concomitant administration of bradycardia-inducing drugs (i.e. beta blockers) may have an additive effect on the slight reduction of heart rate associated with lanreotide. Dose adjustments of such concomitant medications may be necessary.

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

4.6 Fertility, Pregnancy and lactation

Effects on fertility

This drug may produce foetal growth retardation in normal animals, probably due to the suppression of the growth hormone. Fertility studies in normal male and female rats showed that lanreotide decreased fertility index, increased pre-implantation loss and duration of gestation, and decreased the number of delivered pups in the F1 and F2 generations at a systemic exposure level approximately two times higher than in humans. No teratogenic effects were observed in rats or rabbits dosed subcutaneously with lanreotide at doses up to 2 mg/kg/day. Systemic exposure at this dose level was not measured in rabbits, but in rats was about 14 times higher than that expected in humans. In rabbits, embryofetal survival was reduced at doses greater than 0.1 mg/kg/day.

Use in Pregnancy (Category C)

Six pregnancies and one suspected pregnancy have been reported in patients who were being treated with lanreotide. Four pregnancies resulted in healthy full term infants. One acromegalic delivered prematurely due to maternal complications. One patient with acromegaly had a first trimester miscarriage. One additional patient with acromegaly had a suspected first trimester miscarriage. No causal effect has been established between lanreotide and these events.

Use in Lactation

It is not known whether lanreotide is excreted in the milk of animals or humans. A study in rats dosed with lanreotide during lactation showed transitory growth retardation of the offspring prior to weaning, and reduced performance of male offspring in a test of learning and memory. Lanreotide must not be administered to breast feeding women (see section 4.3).

4.7 Effects on ability to drive and use machines

Somatuline Autogel has minor or moderate influence on the ability to drive and use machines. No studies on the effects on the ability to drive and use machines have been performed. However, dizziness has been reported with Somatuline Autogel. If a patient is affected he / she should not drive or operate machinery.

4.8 Undesirable effects

The adverse effects related to Somatuline Autogel during clinical trials are consistent with those seen with other prolonged release formulations of lanreotide, and are predominantly gastrointestinal. In clinical trials of Somatuline Autogel in acromegalic patients, up to 80% of patients experienced at least one adverse effect. More than 50% of these adverse effects were classified as gastrointestinal system disorders. The most commonly reported adverse effects are gastrointestinal disorders and cholelithiasis. The profile of undesirable effects is similar for other indications.

Undesirable effects reported by patients suffering from acromegaly and GEP-NETs, treated with Somatuline Autogel or the microparticle formulation Somatuline LA 30 mg in clinical trials are listed under the corresponding body organ systems according to the following classification: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$).

Acromegaly:

System Organ Class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$).
<i>Metabolism and nutrition disorders</i>		Hypoglycaemia	Diabetes mellitus aggravated, hyperglycaemia
<i>Psychiatric disorders</i>			Insomnia
<i>Nervous system disorders</i>		Dizziness, headache	
<i>Cardiac disorders</i>		Sinus bradycardia	
<i>Vascular disorders</i>			Hot flush
<i>Gastrointestinal disorders</i>	Diarrhoea, loose stools, abdominal pain	Nausea, vomiting, dyspepsia, flatulence, abdominal distension, abdominal discomfort, constipation	Faeces discoloured
<i>Hepatobiliary disorders</i>	Cholelithiasis	Biliary dilatation	
<i>Skin and subcutaneous tissue disorders</i>		Alopecia, hypotrichosis	
<i>General disorders and administration site conditions</i>		Fatigue, injection site reactions (pain, mass, induration, nodule, pruritus)	Asthenia

<i>Investigations</i>		ALAT increased, ASAT abnormal, ALAT abnormal, blood bilirubin increased, blood glucose increased, glycosylated haemoglobin increased, weight decreased	ASAT increased, blood alkaline phosphatase increased, blood bilirubin abnormal, blood sodium decreased
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GEP-NETs:

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100).
<i>Metabolism and nutrition disorders</i>		Hypoglycaemia, diabetes mellitus aggravated, hyperglycaemia, decreased appetite	
<i>Nervous system disorders</i>		Dizziness, headache, lethargy	
<i>Gastrointestinal disorders</i>	Diarrhoea	Abdominal pain, nausea, vomiting, dyspepsia, flatulence, abdominal distension, constipation, steatorrhoea	
<i>Hepatobiliary disorders</i>	Cholelithiasis		
<i>Musculoskeletal and connective tissue disorders</i>		Musculoskeletal pain, myalgia	
<i>Skin and subcutaneous tissue disorders</i>		Alopecia	
<i>General disorders and administration site conditions</i>		Fatigue, injection site reactions (pain, mass, induration, nodule, pruritus), asthenia	
<i>Investigations</i>		Pancreatic enzymes decreased, weight decreased	

Post-marketing safety experience

Gastrointestinal disorders: Unknown: pancreatitis

Hepatobiliary disorders: Unknown: cholecystitis, cholangitis

Immune System Disorders: Unknown: A small number of allergic reactions associated with lanreotide (including angioedema, anaphylaxis, hypersensitivity) have been reported.

Infections and infestations: Unknown: Injection site abscess

Rarely post-injection episodes of malaise with signs of dysautonomia were reported. Rare cases of persisting induration at injection site were reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Animal data do not predict any effects other than those on insulin and glucagon secretion and the gastrointestinal system. If overdosage occurs, symptomatic management is indicated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

One spontaneous report of an overdose of Somatuline LA was reported in a 52 year old patient, with a medical history of diabetes mellitus and hypertension, who had received as a result of drug misuse 30 mg lanreotide per day for 2 months. No acute symptoms or pharmacological signs of overdose were reported. The patient died of an acute myocardial infarction, one week after the last dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigrowth hormones. ATC code: H01C B03.

Like natural somatostatin, lanreotide is a peptide inhibitor of a number of endocrine, neuroendocrine, exocrine and paracrine functions. It shows good affinity for peripheral somatostatin receptors (anterior pituitary and pancreatic). In contrast, its affinity for central receptors is much lower. This profile confers a good specificity of action at the level of growth hormone secretion.

Lanreotide shows a much longer duration of action than natural somatostatin. In addition, its marked selectivity for the secretion of growth hormone, compared to that of insulin, makes it a suitable candidate for the treatment of acromegaly.

Additionally, in the pivotal trial Study 726, lanreotide decreased the levels of plasma chromogranin A and urinary 5-HIAA (5 Hydroxyindolacetic acid) by at least 50% in 42.2% and 53.3%, respectively, of patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs) and with elevated levels of these tumour markers.

Clinical trials

Acromegaly

One open multicentre clinical study was conducted in order to evaluate the efficacy of three repeated deep subcutaneous administrations of Somatuline Autogel (60, 90 or 120 mg) at fixed doses in acromegalic patients previously treated with Somatuline LA, the 30 mg prolonged release microparticle formulation. This study was of a switch design in which acromegalic patients were given Somatuline LA in a first period and Somatuline Autogel in a second period. In the second period, patients received either Somatuline Autogel 60, 90 or 120 mg for three months depending on their respective dosing interval of Somatuline LA, as follows:

- dosing interval of Somatuline LA between 12 and 16 days at the end of the first period: switch to Somatuline Autogel 60 mg.
- dosing interval of Somatuline LA between 8 and 11 days at the end of the first period: switch to Somatuline Autogel 90 mg.
- dosing interval of Somatuline LA between 5 and 7 days at the end of the first period: switch to Somatuline Autogel 120 mg.

This ensured that patients continued to receive the same monthly total lanreotide dose. The lanreotide serum levels in patients at the end of the 3rd interval of Somatuline Autogel administration were similar to those obtained at the end of the 4th interval of administration of Somatuline LA, all strengths combined ($2.17 \pm 0.92 \mu\text{g/L}$ and $2.37 \pm 1.13 \mu\text{g/L}$, respectively). It should be noted that lanreotide serum levels fell in the first interval following changeover to the Autogel formulation, with associated increases in GH and IGF-1 levels.

The study demonstrated that the efficacy of Somatuline Autogel after three injections given every 28 days is not inferior to Somatuline LA (administered every 7 to 14 days) after four injections. Median GH and median IGF-1 were similar at the end of the 3rd interval of Somatuline Autogel and at the end of the 4th interval of Somatuline LA administration. Similar safety was observed after three injections of Somatuline Autogel and after four injections of Somatuline LA.

Median trough GH and IGF-1 levels (µg/L) after treatment with Somatuline LA compared with median GH and IGF-1 levels after treatment with Somatuline Autogel every 28 days for 3 months

Somatuline Autogel dose	End 4th interval Somatuline LA	End 3rd interval Somatuline Autogel
GH (µg/L)		
All doses (n = 107)	2.53	2.21
60 mg (n = 52)	2.37	1.88
90 mg (n = 34)	2.14	2.31
120 mg (n = 21)	3.06	3.59
IGF-1 (µg/L)		
All doses (n = 107)	296	285
60 mg (n = 52)	245	245
90 mg (n = 34)	300	276
120 mg (n = 21)	408	359

Carcinoid Syndrome

One open multicentre clinical study was conducted to evaluate the efficacy of Somatuline Autogel (60 mg, 90 mg or 120 mg) administered once monthly for 6 months in the relief of the clinical symptoms associated with carcinoid syndrome. Each patient's target symptom (diarrhoea or flushing) was chosen by the investigator as the symptom which most troubled the patient. Responders were defined as having a reduction of ≥ 50% (compared to baseline) in the average number of daily episodes of diarrhoea or moderate to severe flushing.

Twenty seven out of 71 patients (38%) in the ITT population and 14/35 (40%) patients in the PP population were target symptom responders at month 6. Of 40 patients whose target symptom was diarrhoea, seven (18%) responded at month 6. Of 31 patients whose target symptom was flushing, twenty (65%) responded at month 6. Somatuline Autogel was generally well tolerated.

Gastroenteropancreatic Neuroendocrine Tumours (GEP-NETs)

A Phase III, 96-week, fixed duration, randomized, double-blind, multi-center, placebo-controlled trial of Somatuline Autogel (Study 726) was conducted in patients with gastroenteropancreatic neuroendocrine tumours to assess the antiproliferative effect of lanreotide.

Patients had metastatic and /or locally advanced inoperable disease with histologically confirmed well or moderately well differentiated tumours primarily localized in the pancreas, mid-gut, hind-gut or of unknown primary location.

Randomization was stratified by previous therapy at entry and the presence/absence of progression at baseline as assessed by RECIST 1.0 (Response Evaluation Criteria in Solid Tumours) during a 3 to 6 month screening phase.

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. Analysis of PFS utilized independent centrally-reviewed radiological assessment of progression. Secondary endpoints included safety, overall survival, percentage of patients alive and progression free at weeks 48 and 96 and effect on tumour markers.

Patients were randomized 1:1 to receive either Somatuline Autogel 120 mg every 28 days (n=101) or placebo (n=103). In terms of age and sex demographics were well balanced (median age 62.7 years, 52.5% male). Additionally, 96% of the patients were Caucasian, 69% of the patients had Grade 1 tumours and 30% had Grade 2, 50.5% of the patients had Ki67 ≤ 2% and 29% had a Ki67 between 2 and 10% (the information on Ki67 was not available in 20% of the patients), 52.5% of the patients had hepatic tumour load ≤10%, 14.5% had hepatic tumour load > 10 and ≤ 25% and 33% had hepatic tumour load > 25%.

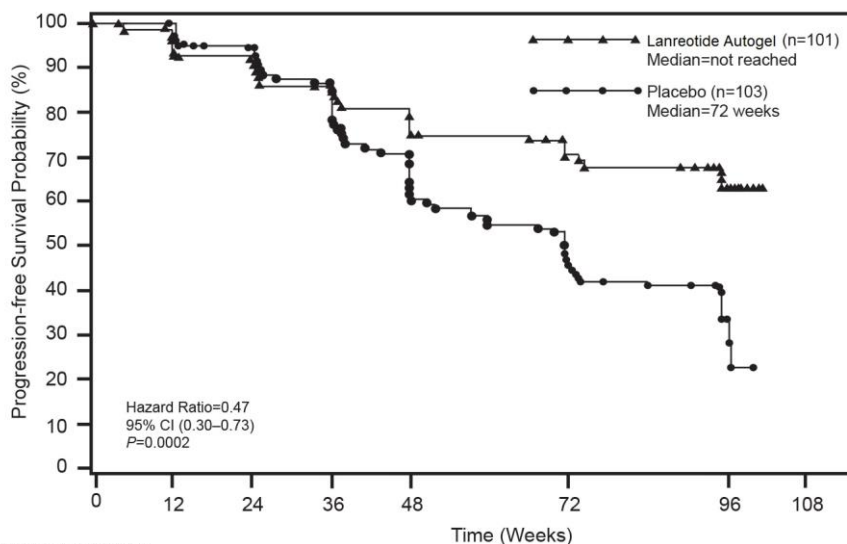
Crossover from placebo to open-label Somatuline Autogel, in the extension study, occurred in 45.6% (47/103) of the patients. Monthly treatment with Somatuline Autogel demonstrated a statistically significant improvement in PFS resulting in a 53% reduction in risk of disease progression or death when compared to placebo (p=0.0002). The median duration of PFS for Somatuline Autogel was not reached at 96 weeks, while the median duration of PFS for placebo was 72 weeks as shown in Table 1 and Figure 1.

Table 1: Efficacy results of the Phase III study

Median Progression free survival (weeks)		Hazard Ratio (95% CI)	Reduction in risk of progression or death	p-value
Somatuline Autogel (n=101)	Placebo (n=103)			
> 96 weeks	72.00 weeks (95% CI : 48.57, 96.00)	0.470 (0.304, 0.729)	53% *	0.0002

* based on 32 events including 2 deaths in the Somatuline Autogel group and 60 events including 2 deaths in the placebo group.

Figure 1: Kaplan-Meier Progression Free Survival Curves



Number of subjects still at risk

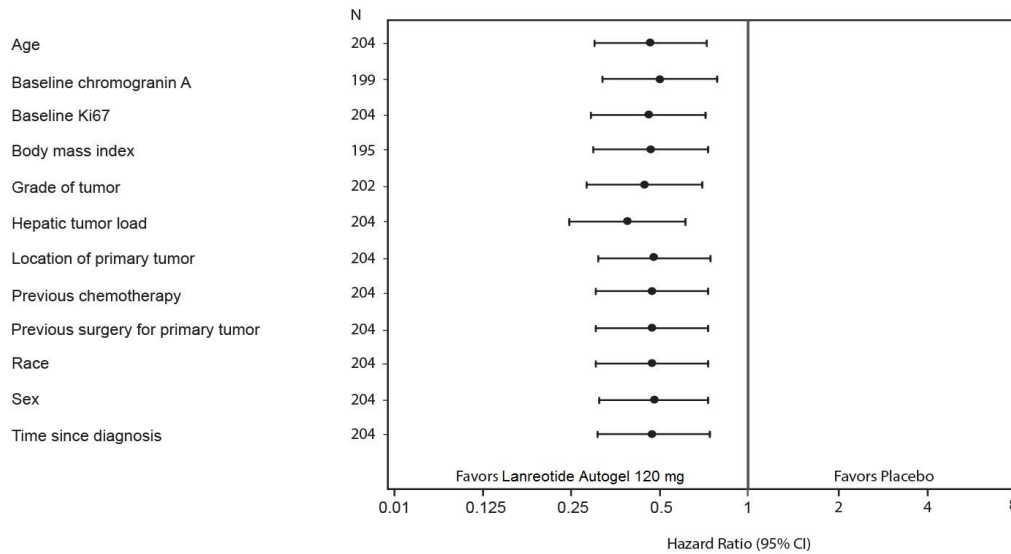
Lanreotide Autogel	101	94	84	78	71	61	40	0
Placebo	103	101	87	76	59	43	26	0

Based on the Kaplan Meier (KM) estimates at the time of the last scan performed 78% of subjects treated with placebo had progressed or died compared with 38% of subjects treated with Somatuline Autogel.

The beneficial effect of lanreotide in reducing the risk of progression or death was statistically

confirmed in some pre-planned baseline covariates (Figure 2).

Figure 2: Pre-planned Exploratory Covariate Analysis of PFS: HRs for Treatment from Individual Models and Final Multivariate Model – ITT population

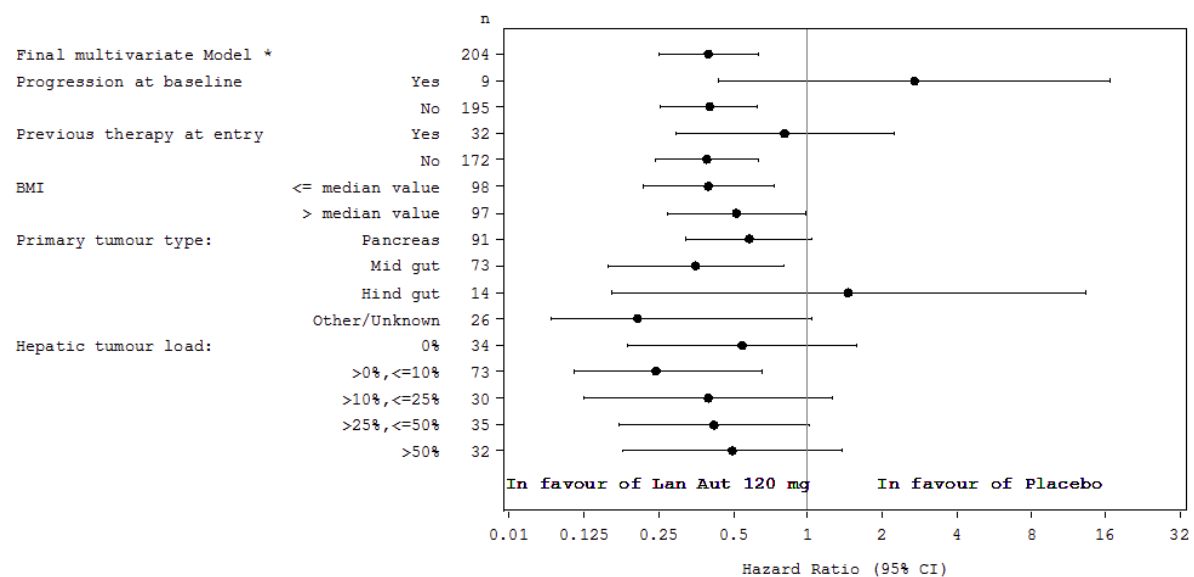


Note: All HRs are the relative hazard for lanreotide Autogel vs placebo. The results for covariates are derived from separate Cox PH models with terms for treatment, progression at baseline, previous therapy at entry, and the term labeled on the vertical axis.
 Baseline Ki67 was not assessed in 20.1% of patients

A clinically-relevant benefit of treatment with Somatuline Autogel was seen in patients with tumours of pancreatic, midgut and other/unknown origin as in the overall study population. The limited number of patients with hindgut tumours (14/204) contributed to difficulty in interpreting the results in this subgroup. The available data suggested no benefit of lanreotide in these patients.

A beneficial effect of lanreotide in reducing the risk of progression or death could not be shown for some covariates - progression at baseline (n=9, p= 0.29), previous therapy at entry (n=32, p=0.68), hind-gut (n=14, p=0.73), BMI > median value (n=97, p=0.05), hepatic tumour load categories = 0% or > 10% (n's ≤ 35, p> 0.05), as shown in Figure 3.

Figure 3 - Exploratory Covariate Analysis of PFS: Post-Hoc Subgroup Analysis for Terms in the Final Multivariate Model - ITT Population



Changes in tumour size were also assessed during the study. Forty-nine (50.5%) patients in the Somatuline Autogel group compared to 18 (17.8%) in the placebo group experienced tumour shrinkage at some time during the study. Eighteen (18.6%) patients in the Somatuline

Autogel group compared to 20 (19.8%) in the placebo group experienced a minimal change in tumour size of less than 1%. An increase in tumour size was observed in 30 (30.9%) in the group treated with Somatuline Autogel and in 63 (62.4%) patients in the placebo group.

No significant difference in overall survival was found in the pivotal Study 726 between the placebo arm and the Somatuline Autogel arm.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lanreotide after intravenous administration in healthy volunteers indicated limited extravascular distribution, with a steady-state volume of distribution of 13 L. Total clearance was 20 L/h, terminal half-life was 2.5 hours and mean residence time was 0.68 hours.

After a single subcutaneous injection of Somatuline Autogel 60 mg in healthy volunteers, a maximum serum concentration (C_{max}) of 5.8 ± 4 ng/mL was reached after 6 hours, followed by a slow decrease (mean residence time: 30 ± 6 days, apparent half-life: 33 ± 14 days). The absolute bioavailability was $63 \pm 10\%$.

After a single intramuscular injection of Somatuline Autogel 60 mg in healthy volunteers, a maximum serum concentration (C_{max}) of 6.8 ± 3 ng/mL was reached after 15 hours, followed by a slow decrease (mean residence time: 23 ± 11 days, apparent half-life: 23 ± 9 days). The absolute bioavailability was $79 \pm 10\%$.

Therefore the route of administration (subcutaneous or intramuscular) does not show any marked influence on the lanreotide pharmacokinetic profile.

After a single intramuscular injection of Somatuline Autogel 90 mg in healthy volunteers, a maximum serum concentration (C_{max}) of 9.8 ± 5 ng/mL was reached after 10 hours, followed by a slow decrease (mean residence time: 26 ± 4 days, apparent half-life: 31 ± 16 days). The absolute bioavailability was $58 \pm 10\%$.

After a single intramuscular injection of Somatuline Autogel 120 mg in healthy volunteers, a maximum serum concentration (C_{max}) of 12.8 ± 7 ng/mL was reached after 16 hours, followed by a slow decrease (mean residence time: 29 ± 3 days, apparent half-life: 28 ± 6 days). The absolute bioavailability was $55 \pm 10\%$.

Therefore lanreotide serum concentration after intramuscular administration of Somatuline Autogel 60, 90 and 120 mg shows an almost log-linear first order lanreotide release profile.

In an open, comparative, multicentre, switch design study, Somatuline Autogel 120 mg was administered every 56, 42 or 28 days to those given Somatuline LA 30 mg every 14, 10 or 7 days at least for 2 months prior to the study. This study demonstrated that trough levels obtained after the switch were similar to levels with Somatuline LA treatment. Furthermore, the serum levels obtained after administration of Somatuline Autogel 120 mg every 56, 42 or 28 days are comparable, at equivalent cumulative dose, to those obtained after three deep subcutaneous injections of Somatuline Autogel 60, 90 or 120 mg, respectively given every 28 days.

In a population PK analysis in 290 GEP-NET patients receiving Somatuline Autogel 120 mg, rapid initial release was seen with mean C_{max} values of 7.49 ± 7.58 ng/mL reached within the first day after a single injection. Steady-state concentrations were reached after 4 to 5 injections of Somatuline Autogel 120 mg every 28 days 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 clearance was 513 L/day (21.4 L/H) for a typical 74 kg individual and the mean apparent terminal half-life was 43.6 days.

5.3 Preclinical safety data

Genotoxicity

Lanreotide did not show mutagenic or clastogenic activity in a standard battery of in vitro and in vivo tests.

Carcinogenicity/ Mutagenicity

Two carcinogenicity studies were conducted by the subcutaneous route in mice and rats at doses up to 30 and 0.5 mg/kg/day respectively. Lanreotide did not increase tumour incidences at doses up to 5 mg/kg/day in male mice and 1.5 mg/kg/day in female mice (relative exposure based on animal:human serum AUC, ≤ 12) and at 0.1 mg/kg/day in rats (relative exposure, ≤ 1). Injection site tumours (fibroma, fibrosarcoma and/or malignant fibrous histiocytoma) were increased in incidence at higher doses (relative exposure, ≥ 18 in mice and ≥ 2 in rats). The development of these tumours is consistent with chronic irritation / inflammation in rodents from repeated injection and they are not considered to indicate a carcinogenic hazard to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sterile water for injection and glacial acetic acid (for pH adjustment).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at 2°C - 8°C (Refrigerate. Do not freeze) in the original package.

Once removed from the refrigerator, product left in its sealed pouch may be returned to the refrigerator (the number of temperature excursions must not exceed three times) for continued storage and later use, provided it has been stored for no longer than a total of 24 hours at below 40°C.

6.5 Nature and contents of container

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

Each ready to use pre-filled syringe is placed into a plastic tray and packed in a laminated pouch and is contained in a cardboard box.

Box of one 0.5 mL pre-filled syringe and one needle (1.2 mm x 20 mm).

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand
Toll-Free Phone: 0800 947 486

9. DATE OF FIRST APPROVAL

19 October 2017

10. DATE OF REVISION OF THE TEXT

23 June 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.4 Special precautions for storage	Addition of temperature excursions outside of refrigerator
6.5 Nature and contents of container	Update to describe new syringe

Somatuline[®] is a registered trademark of Ipsen.