New Zealand Data Sheet

1 MYTOLAC®

MYTOLAC 60 mg, solution for injection in a pre-filled syringe
MYTOLAC 90 mg, solution for injection in a pre-filled syringe
MYTOLAC 120 mg, solution for injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe.

It is a white to pale-yellow semi-solid formulation practically free of foreign particles. It 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.

The formulation contains water for injections and glacial acetic acid (for pH adjustment) as excipients. The pH of Mytolac solution is 5.7 to 6.3.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mytolac 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 (neuroendocrine) 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 Dose and method of administration

Posology

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

In patients previously treated with lanreotide microparticle formulation once every 14 days, the initial dose of Mytolac should be 60 mg every 28 days; in patients previously treated with lanreotide microparticle formulation once every 10 days, the initial dose of Mytolac should be 90 mg every 28 days, and in patients treated with lanreotide microparticle formulation once every 7 days, the initial dose of Mytolac 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 Mytolac 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 Mytolac is one injection of 120 mg administered every 28 days. The treatment with Mytolac 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 lanrerotide. 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

Mytolac 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 lanreotide, 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 lanreotide 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 aluminium 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 aluminium 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 insert.

4.3 Contraindications

Mytolac should not be prescribed during lactation, nor in patients presenting with hypersensitivity to the peptide or related peptides or any of the excipients (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

Hyperglycaemia and Hypoglycaemia
Pharmacological studies in animals and humans show that lanreotide, like somatostatin and its analogues inhibit secretion of insulin and glucagon. Hence, patients treated with lanreotide 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.

Hypothyroidism
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.

Cholelithiasis and Complications of Cholelithiasis
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 post-marketing 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 section 4.2 Dose and method of administration, *'Use in renal or hepatic impairment'*).

Bradycardia
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 lanreotide 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.

Pancreatic function
Pancreatic exocrine insufficiency (PEI) has been observed in some patients receiving lanreotide therapy for gastroenteropancreatic neuroendocrine tumours. Symptoms of PEI can include steatorrhea, loose stools, abdominal bloating and weight loss. Screening and appropriate treatment for PEI according to clinical guidelines should be considered in symptomatic patients.

Paediatric Use
As there is no experience of the use of the product in children, the use of lanreotide in children cannot be advised.

Use in 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 lanreotide may result in the reduction of the intestinal absorption of co-administered drugs. As with other somatostatin analogues, lanreotide 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

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.

Use in Pregnancy (Category C)

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of lanreotide in pregnant women.
Studies in animals have shown reproductive toxicity but no evidence of teratogenic effects. The potential risk for humans is unknown.

As a precautionary measure, it is preferable to avoid the use of lanreotide during pregnancy.

This drug may produce foetal growth retardation in normal animals, probably due to the suppression of the growth hormone. No teratogenic effects were observed in rats or rabbits dosed subcutaneously with lanreotide at doses up to 2mg/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 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 Contraindications).

4.7 Effects on ability to drive and use machines

Lanreotide 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 lanreotide. If a patient is affected he /she should not drive or operate machinery.

4.8 Undesirable effects

The adverse effects related to lanreotide solution for injection during clinical trials are consistent with those seen with other prolonged release formulations of lanreotide, and are predominantly gastrointestinal. In clinical trials of lanreotide solution for injection 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 lanreotide solution for injection or the microparticle formulation of lanreotide 30 mg in clinical trials are listed under the corresponding body organ systems according to the following classification: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100): not known (cannot be estimated from the available data).

Table 1: Reported Adverse Effects

System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100).	Post-marketing safety experience (frequency not known)
Immune system disorders				Allergic reactions (including angioedema, anaphylaxis, hypersensitivity)
Metabolism and nutrition disorders		Hypoglycaemia, decreased appetite**, hyperglycaemia, diabetes mellitus	Diabetes mellitus aggravated, hyperglycaemia	
Psychiatric disorders			Insomnia*	
Nervous system disorders		Dizziness, headache, lethargy**		
Cardiac disorders		Sinus bradycardia*		
Vascular disorders			Hot flush*	
Gastrointestinal disorders	Diarrhoea, loose stools*, abdominal pain	Nausea, vomiting, dyspepsia, flatulence, abdominal distension, abdominal discomfort*, constipation, steatorrhoea**	Faeces discolored*	Pancreatic exocrine insufficiency, pancreatitis
Hepatobiliary disorders	Cholelithiasis	Biliary dilatation*		cholecystitis, cholangitis
Skin and subcutaneous tissue disorders		Alopecia, hypotrichosis*		
Musculoskeletal and connective tissue disorders		Musculoskeletal pain**, myalgia**		
General disorders and administration site conditions		Asthenia, Fatigue, injection site reactions (pain, mass, induration, nodule, pruritus)		Injection site abscess
Investigations		ALAT increased*, ASAT abnormal*, ALAT abnormal*, Blood bilirubin increased*, blood glucose increased*, glycosylated haemoglobin increased*, weight decreased, pancreatic enzymes decreased**	ASAT increased*, blood alkaline phosphatase increased*, blood bilirubin abnormal*, blood sodium decreased*	

* based on a pool of studies conducted in acromegalic patients
** based on a pool of studies conducted in patients with GEP-NETs

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 medicine 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://pophealth.my.site.com/carmreportnz/s/.

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.

One spontaneous report of an overdose of lanreotide 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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
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 efficacy

Acromegaly

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

- dosing interval of lanreotide microparticle formulation between 12 and 16 days at the end of the first period: switch to lanreotide solution for injection 60 mg.
- dosing interval of lanreotide microparticle formulation between 8 and 11 days at the end of the first period: switch to lanreotide solution for injection 90 mg.
- dosing interval of lanreotide microparticle formulation between 5 and 7 days at the end of the first period: switch to lanreotide solution for injection 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 lanreotide solution for injection administration were similar to those obtained at the end of the 4th interval of administration of lanreotide microparticle formulation, all strengths combined (2.17 ± 0.92 µg/L and 2.37 ± 1.13 µg/L, respectively). It should be noted that lanreotide serum levels fell in the first interval following changeover to the solution for injection formulation, with associated increases in GH and IGF-1 levels.

The study demonstrated that the efficacy of lanreotide solution for injection after three injections given every 28 days is not inferior to lanreotide microparticle formulation (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 lanreotide solution for injection and at the end of the 4th interval of lanreotide microparticle formulation administration. Similar safety was observed after three injections of lanreotide solution for injection and after four injections of lanreotide microparticle formulation.

Median trough GH and IGF-1 levels (µg/L) after treatment with lanreotide microparticle formulation compared with median GH and IGF-1 levels after treatment with lanreotide solution for injection every 28 days for 3 months

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

Carcinoid syndrome

One open multicentre clinical study was conducted to evaluate the efficacy of lanreotide solution for injection (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.

27 out of 71 patients (38%) in the ITT population and 14 out of 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. lanreotide solution for injection 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 lanreotide solution for injection (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 lanreotide solution for injection 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%.

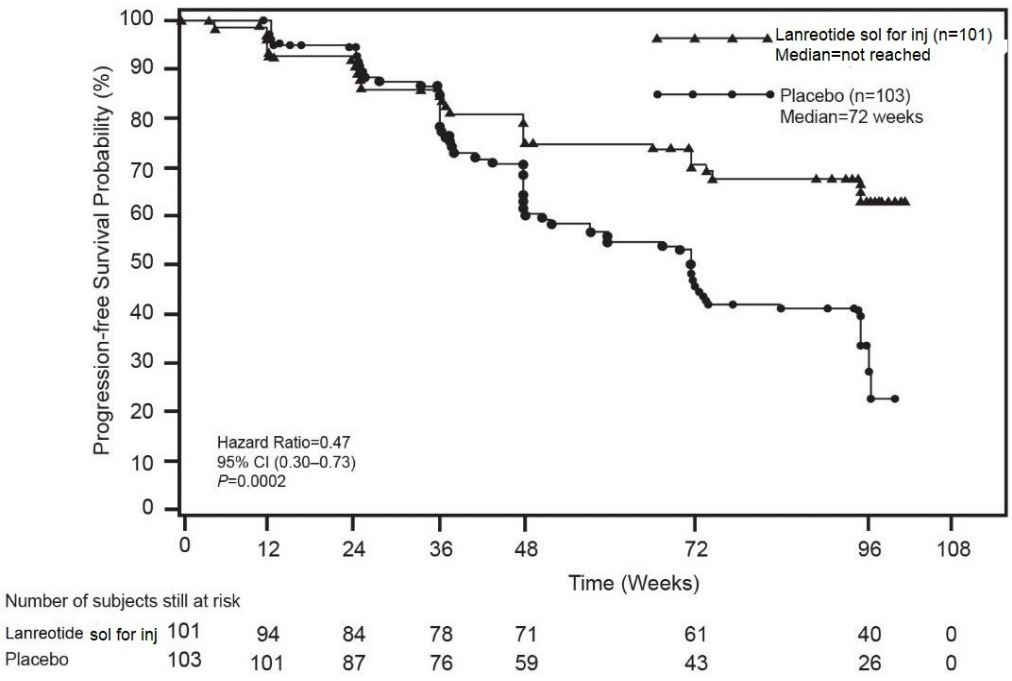
Crossover from placebo to open-label lanreotide solution for injection, in the extension study, occurred in 45.6% (47/103) of the patients. Monthly treatment with Somatuline Autogel demonstrated a statistically significant improvement in PFS resulting in a 53% reduction in risk of disease progression or death when compared to placebo (p=0.0002). The median duration of PFS for lanreotide solution for injection was not reached at 96 weeks, while the median duration of PFS for placebo was 72 weeks as shown in Table 4 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
Lanreotide solution for injection (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 lanreotide solution for injection group and 60 events including 2 deaths in the placebo group*

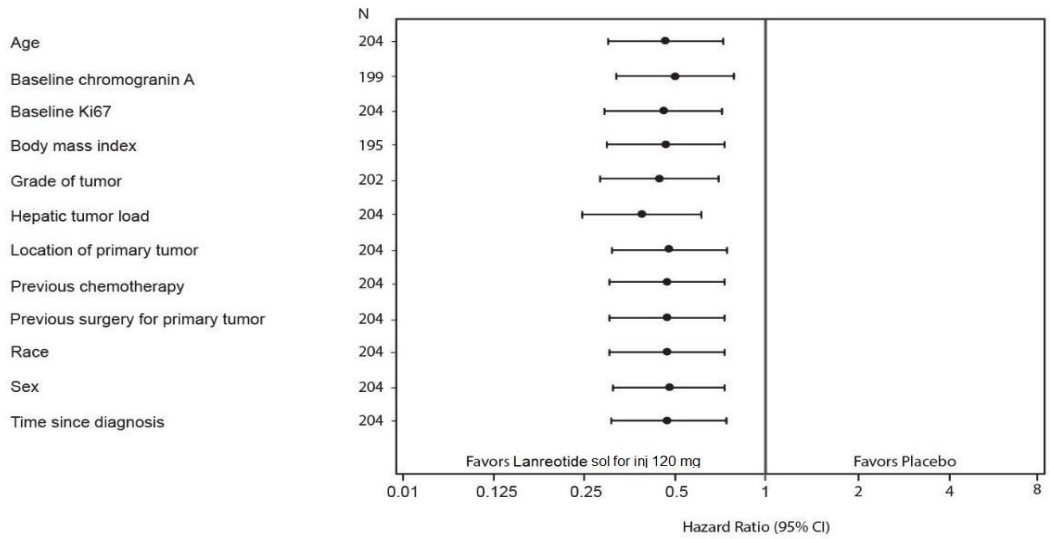
Figure 1: Kaplan-Meier Progression Free Survival Curves



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 lanreotide solution for injection.

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

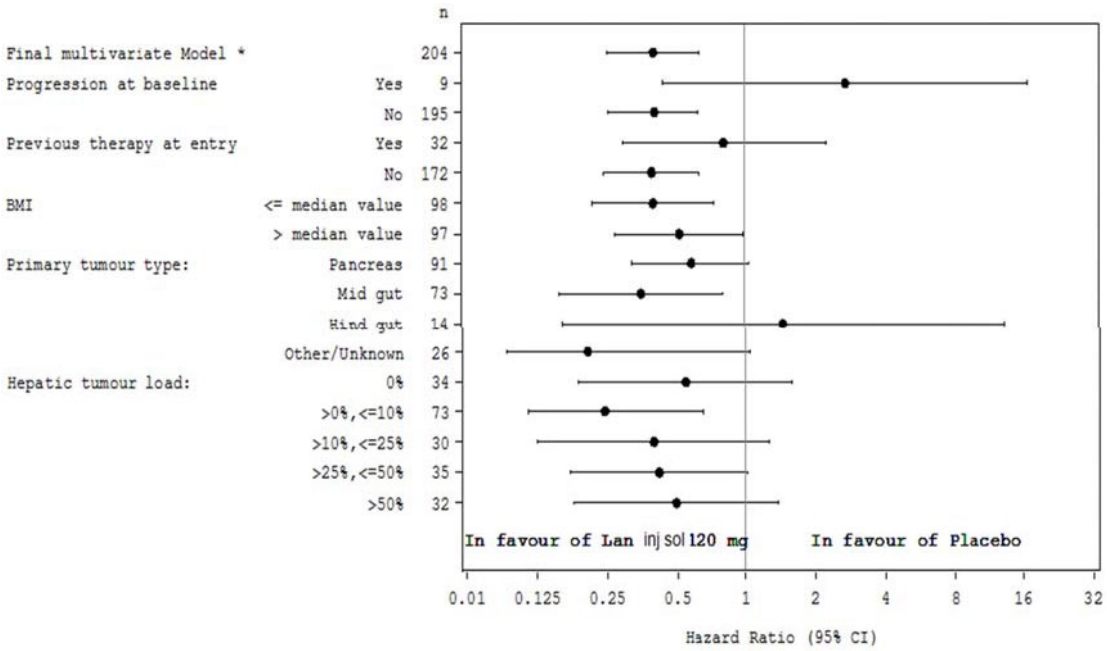


Note: All HRs are the relative hazard for lanreotide sol for inj vs placebo. The results for covariates are derived from separate Cox PH models with terms for treatment, progression at baseline, previous therapy at entry, and the term labeled on the vertical axis.
Baseline Ki67 was not assessed in 20.1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

A clinically-relevant benefit of treatment with lanreotide solution for injection 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 lanreotide solution for injection 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 lanreotide solution for injection 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 lanreotide solution for injection 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 lanreotide solution for injection 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 lanreotide solution for injection 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 ± 10%.

After a single intramuscular injection of lanreotide solution for injection 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 ± 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 lanreotide solution for injection 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 ± 10%.

After a single intramuscular injection of lanreotide solution for injection 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 ± 10%.

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

In an open, comparative, multicentre, switch design study, lanreotide solution for injection 120 mg was administered every 56, 42 or 28 days to those given lanreotide microparticle 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 lanreotide microparticle treatment. Furthermore, the serum levels obtained after administration of lanreotide solution for injection 120 mg every 56, 42 or 28 days are comparable, at equivalent cumulative dose, to those obtained after three deep subcutaneous injections of lanreotide solution for injection 60, 90 or 120 mg, respectively given every 28 days.

In a population PK analysis in 290 GEP-NET patients receiving lanreotide solution for injection 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 lanreotide solution for injection 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

Water for injections.

Glacial acetic acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at 2°C - 8°C (refrigerate, do not freeze). Protect from light.

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 72 hours at below 40°C.

6.5 Nature and contents of container

Mytolac is supplied in a pre-filled syringe (polypropylene with thermoplastic elastomer rubber plunger stopper sealed with polypropylene cap) which is placed in a plastic tray and sealed inside an aluminum pouch. A separately packed automatic single use safety needle (stainless steel) is also provided. Both are packaged inside a cardboard box.

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

6.6 Special precautions for disposal

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

The used injection device should be disposed of in a designated sharps container.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Mercury Pharma (NZ)
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

17 November 2022

10 DATE OF REVISION OF TEXT

11 July 2025

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Shelf life updated to 3 years.
6.4	Increase temperature excursion to 72 hours