Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Somatuline LA 30mg, powder and solvent for prolonged-release suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 30 mg of lanreotide presented as lanreotide acetate.
After reconstitution with the solvent, 1 ml of the suspension contains 15 mg lanreotide as lanreotide acetate.

Each vial contains 2.64 mg of sodium.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged-release suspension for injection.

Powder: A practically white lyophilisate with the presence of bubbles at the top.
Solvent: A clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acromegaly:
Somatuline LA is indicated for the treatment of acromegaly when the circulating levels of Growth Hormone (GH) and/or Insulin-like Growth Factor-I (IGF-I) remain abnormal after surgery and/or radiotherapy, or in patients who require treatment prior to such intervention.

Thyrotropic Adenomas:
Somatuline LA is indicated for the treatment of primary thyrotropic adenomas.

Neuroendocrine Tumours:
Somatuline LA is indicated for the relief of symptoms associated with carcinoid tumours.

Digestive Fistulae:
Somatuline LA is indicated for the treatment of post-operative, simple, externalised, pancreatic, duodenal and small intestine fistulae.

4.2 Posology and method of administration

Adults:

Acromegaly/ Neuroendocrine tumours/Thyrotropic Adenomas

For intramuscular injection only.

Initially, one injection every 14 days. The frequency of injection may be varied in accordance with the individual patient's response (as judged by symptomatology and/or biochemical monitoring). Injection sites should be varied.

Digestive fistulae

Initially, one intramuscular injection should be given to assess the patient's response.

In patients with fistulae volume drainage reduction of at least 50% after 72h, 1 injection should be given every 10 days until closure of the fistula, or up to a maximum of 3 additional injections.

Older People:

In older people, no dosage adjustment is necessary due to the wide therapeutic window of Somatuline LA (see section 5.2).

Paediatric population:

Somatuline LA 30 mg is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Renal and/or hepatic impairment:
In patients with impaired renal or hepatic function, no dosage adjustment is necessary due to the wide therapeutic window of lanreotide (see section 5.2).

4.3 Contraindications

Hypersensitivity to somatostatin or related peptides or any of the excipients listed in 6.1.

4.4 Special warnings and precautions for use

Somatuline LA may reduce gallbladder motility and lead to gallstone formation. Therefore, patients may need to be monitored periodically. 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.

Pharmacological studies in animals and humans show that Somatuline LA, like somatostatin and other somatostatin analogues, inhibits secretion of insulin and glucagon. Hence, patients treated with Somatuline LA may experience hypoglycaemia or hyperglycaemia.

Blood glucose levels should be monitored when Somatuline LA treatment is initiated, or when the dose is altered and any anti-diabetic treatment should be adjusted accordingly.

Somatuline LA should only be used under hospital specialist supervision, with the appropriate facilities available for diagnosis and evaluation of response.

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.

In patients without underlying cardiac problems Somatuline LA may lead to a decrease of heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to Somatuline LA treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with lanreotide in patients with bradycardia (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interactions

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

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

Interactions with highly plasma bound drugs are unlikely in view of the moderate binding of lanreotide to serum proteins.

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

Concomitant administration of bradycardia inducing drugs (e.g. beta blockers) may have an additive effect on the slight reduction of heart rate associated with Somatuline LA. 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 the suppression of growth hormone.

Since it cannot be excluded that Somatuline LA may have this effect, other drugs mainly metabolized 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

Pregnancy
Non clinical data:
Studies in animals showed no evidence of teratogenic effects associated with lanreotide during organogenesis.
Reduced fertility was observed in female rats due to the inhibition of GH secretion at doses in excess of those achieved in humans at therapeutic doses.

Clinical data:
Data on a limited number of exposed pregnancies indicate no adverse effects of lanreotide on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available.

Because animal studies are not always predictive of human responses, Somatuline LA should be administered to pregnant women only if clearly needed.

Breast-feeding
It is not known whether this drug is excreted in human milk.
Because many drugs are excreted in human milk, caution should be exercised when lanreotide is administered during lactation.

4.7 Effects on ability to drive and use machines

While no effect on the ability to drive and use machines has been established, dizziness has been reported with Somatuline LA 30 mg. If a patient is affected, he/she should not drive or operate machinery.

4.8 Undesirable effects

Undesirable effects reported by patients suffering from acromegaly and gastroenteropancreatic neuroendocrine tumours (GEP-NETs) treated with lanreotide 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).

The most commonly expected adverse drug reactions following treatment with lanreotide are gastrointestinal disorders (most commonly reported are diarrhoea and abdominal pain, usually mild or moderate and transient), cholelithiasis (often asymptomatic) and injection site reactions (pain, nodules and induration).

The profile of undesirable effects is similar for all indications.

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)**
Infections and infestations				Injection site abscess
Metabolism and nutrition disorders		Hypoglycaemia, decreased appetite**, hyperglycaemia, diabetes mellitus		
Psychiatric disorders			Insomnia*	
Nervous system disorders		Dizziness, headache, lethargy**		
Cardiac disorders		Sinus bradycardia*		
Vascular disorders			Hot flush*	
Gastrointestinal disorders	Diarrhoea, loose stools*,	Nausea, vomiting, constipation, flatulence, abdominal distension, abdominal discomfort*, dyspepsia,	Faeces discoloured*	Pancreatitis

	abdominal pain	steatorrhoea**		
Hepatobiliary disorders	Cholelithiasis	Biliary dilatation*		Cholecystitis Cholangitis
Musculoskeletal and connective tissue disorders		Muskuloskeletal pain**, myalgia**		
Skin and subcutaneous tissue disorders		Alopecia, hypotrichosis*		
General disorders and administration site conditions		Asthenia, fatigue, injection site reactions (pain, mass, induration, nodule, pruritus)		
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*	
Immune System Disorders				Allergic reactions (including angioedema, anaphylaxis, hypersensitivity)

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

Reporting of suspected adverse reactions
Reporting of 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigrowth hormones,

ATC code: H01C B03.

Lanreotide is an octapeptide analogue of natural somatostatin. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions. Lanreotide has a high affinity for human somatostatin receptors (SSTR) 2 and 5 and a reduced binding affinity for human SSTR1, 3, and 4. Activity at human SSTR 2 and 5 is the primary mechanism believed responsible for GH inhibition.

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. By inhibiting the synthesis of thyroid stimulating hormone, lanreotide also normalised the thyroid function of patients with thyrotrophin-secreting adenomas. Furthermore, the inhibitory action of lanreotide on intestinal exocrine secretion, digestive hormones and cellular proliferation mechanisms is suited to the symptomatic treatment of endocrine digestive tumours, especially carcinoids.

Lanreotide, like somatostatin, exhibits a general exocrine anti-secretory action. It inhibits the basal secretion of motilin, gastric inhibitory peptide and pancreatic polypeptide, but has no significant effect on fasting secretin or gastrin secretion. Lanreotide markedly inhibits meal-induced increases in superior mesenteric artery blood flow and portal
venous blood flow. Lanreotide significantly reduces prostaglandin E1-stimulated jejunal secretion of water, sodium, potassium and chloride. Lanreotide reduces prolactin levels in acromegalic patients treated long term.

Lanreotide is clearly more active than natural somatostatin and shows a much longer duration of action.

During a randomised, double-blind clinical study involving patients with digestive fistulae, 64.8% of the patients who received one i.m. injection of lanreotide were responders (i.e. presented a reduction of the drainage volume of fistulae of at least 50% within 72 hours) versus 37.7% of patients treated with placebo. In this subgroup of responder patients and upon continuation of the treatment (one i.m injection every 10 days), median fistula closure time was 14 days in patients treated with lanreotide PR 30mg versus 17 days in patients treated with placebo.

A randomised, placebo-controlled study has investigated the effects of Somatuline LA 30 mg administration every 10 days on top of concomitant treatment regimen including intravenous corticoids, proton-pump inhibitors, antispasmodics, antiemetics and analgesics, in 80 patients with upper intestinal obstruction of malignant origin due to confirmed peritoneal carcinomatosis in palliative care, having at least 2 vomiting episodes per day or a nasogastric tube and for whom, according to recent surgical advice, surgery was inappropriate. Patients having a bowel obstruction which could be explained by a non-malignant cause were excluded from the study. The primary objective was to assess the proportion of responders 7 days after a single injection of Somatuline LA 30mg versus placebo. Treatment response was defined as 1 or less vomiting episode per day for at least 3 consecutive days or no vomiting recurrence for at least 3 consecutive days for subjects in whom nasogastric tube had been removed.

In the Intent-to-Treat [ITT] population, when based on subject diary record cards (DRC) assessed at day 7, the responders rate was more favourable for lanreotide than placebo although not statistically significant (41.9% [18/43] versus 29.7% [11/37], odds ratio=1.75 [95% CI 0.68, 4.49, p=0.24]). In the Per Protocol (PP) population a significantly higher responders' rate, based on DRC data, was observed for lanreotide when compared to placebo (57.7% [15/26] and 30.4% [7/23], respectively [odds ratio=3.60, 95% CI 1.03, 12.62, p=0.045]).
In the ITT population, changes in well-being were assessed using a 100 mm-visual analog scale. Statistically significant improvements in well-being were observed with lanreotide treatment when compared to placebo from baseline to D3, D6 and D7.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Lanreotide PR 30 mg in all subsets of the paediatric population in acromegaly, pituitary gigantism, gastrointestinal fistulae, metastases to peritoneum and pituitary neoplams (see section 4.2 for information on paediatric use). The European Medicines Agency has listed gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma and phaeochromocytoma) on the list of class waivers.

5.2 Pharmacokinetic properties

Intrinsic pharmacokinetic parameters of lanreotide after intravenous administration in healthy volunteers indicated limited extravascular distribution, with a steady-state volume of distribution of 16.1 l. Total clearance was 23.7 l/h, terminal half-life was 1.14 hours and mean residence time was 0.68 hours.

In studies evaluating excretion, less than 5% of lanreotide was excreted in urine and less than 0.5% were recovered unchanged in faeces, indicating some biliary excretion.

The plasma profile of a single dose of Somatuline LA 30 mg administered intramuscularly in healthy volunteers is characterised by an initial rapid release phase, corresponding to the release of peptide bound to the surface of the microspheres, and then

by a second release phase, followed by a very slow decrease induced by the prolonged release of the active substance captured in the microparticles constituting the drug product.

After an initial serum concentration peak of 8.5 ± 4.7 ng/ml obtained between 1 and 2 h after drug administration, serum levels decrease during 1-3 days and then rise from day 3 to 5 until day 14-21 showing a "pseudo plateau" with most of the serum levels around 1ng/mL during this period of time.
This prolonged release behaviour is described by a mean residence time of 15.0 ± 1.6 days and a half-life of 5.0 ± 2.3 days.

The pharmacokinetic profile in acromegalic patients after a single administration of Somatuline LA 30 mg is comparable to that obtained in healthy volunteers.

Pharmacokinetic profile after repeated administration has been also studied in acromegalic patients. Steady state levels is obtained after the 4th consecutive dose presenting a peak of 10.9 ± 4.4 ng/mL around 2 hours after administration and then a "pseudo plateau" followed by a first order kinetics. The mean minimum and average serum concentrations at steady state is 2.2 ± 0.7 and 2.8 ± 0.8 ng/mL respectively and a no relevant accumulation is observed (Rac = 2.2).

Renal/hepatic impairment
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. In subjects with moderate to severe hepatic impairment, a reduction

in clearance was observed (30%). Volume of distribution and mean residence time increased in subjects with all degrees of hepatic insufficiency.

It is not necessary to alter the starting dose in patients with renal or hepatic impairment, as lanreotide serum concentrations in these populations are expected to be well within the range of serum concentrations safely tolerated in healthy subjects.

Older people
Older people show an increase in half-life and mean residence time compared with healthy young subjects. It is not necessary to alter the starting dose in elderly patients, as lanreotide serum concentrations in this population are expected to be well within the range of serum concentrations safely tolerated in healthy subjects.

5.3 Preclinical safety data

In carcinogenic bioassays studies conducted in rats and mice, no systemic neoplastic changes were observed at doses in excess of those achieved in humans at therapeutic doses. Increased incidence of subcutaneous tumours were observed at the injection sites likely due to the increased dose frequency in animals (daily) compared to monthly dosing in humans and therefore may not be clinically relevant.

In *in vitro* and *in vivo* standard battery tests, lanreotide did not show any genotoxic potential.
Resorption of microperes is completed in 45 – 60 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for suspension

Lactide glycolide copolymer
Lactic glycolic copolymer
Mannitol (E421)
Carmellose Sodium (E466)
Polysorbate 80 (E433)

Solvent for suspension

Mannitol (E421)
Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

Unopened: powder for suspension -2 years
solvent for suspension- 3 years

Reconstituted suspension: Use immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C) in the original package. Do not freeze.
For storage conditions of reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder in a vial (type I glass), with a rubber stopper (halogenobutyl) and cap (aluminium) and 2 ml solvent in an ampoule (type I glass).
Box of 1 vial, 1 ampoule, 1 syringe and 2 needles.

6.6 Special precautions for disposal and other handling

The powder should be reconstituted with the solvent immediately before injection, by swirling the vial, gently, without inverting it, until a homogenous suspension with a milky appearance is obtained. **This must not be mixed with othermedications.**

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

For single use only. Discard any unused portion.
Do not use if the kit is damaged or opened.
Dispose of used needles in a designated sharps container.

7 MARKETING AUTHORISATION HOLDER

Ipsen Pharmaceuticals Limited
Blanchardstown Industrial Park
Blanchardstown
Dublin 15
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0869/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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