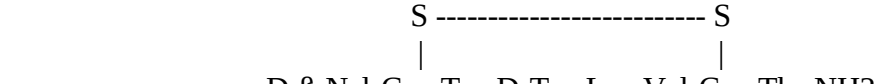
PRODUCT INFORMATION
SOMATULINE LA 30mg

NAME OF MEDICINE
Lanreotide (I.N.N., B.A.N.) *acetate*

DESCRIPTION
Powder for suspension for injection. Somatuline LA is formulated as a prolonged - release depot suspension of lanreotide acetate for intramuscular injection. The slow release properties of the formulation have been achieved by encapsulation of lanreotide in microspheres composed of a biodegradable matrix of copolymers. The gradual degradation of the matrix after injection results in prolonged release of the active drug.

Each vial is filled with a quantity of microparticles which ensures the injection of 30 mg of lanreotide. Lanreotide is a peptide containing eight amino acids as shown below:



Molecular formula : $C_{54}H_{69}N_{11}O_{10}S_2$ CAS : 108736-35-2
Excipients include polyglactin, lactic-glycolic copolymer, mannitol, carmellose sodium, polysorbate 80.

PHARMACOLOGY
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.

Pharmacokinetics
The plasma profile of lanreotide administered intramuscularly as the Somatuline LA prolonged release formulation in healthy volunteers, is characterised by an initial rapid release phase (phase 1) followed by a prolonged slow release phase (phase 2). The plasma peak (C_{max}: 8.5 ± 4.7mg/l) occurs between 1 and 2 hours post-dosing. It is followed by a decay during the days 1-3 post administration and a slight increase from approximately days 3-5 to days 14-21 post dosing, showing a pseudo plateau profile around 1 mg/l during this period of time. Approximately 7 % of the dose is released during the first day after injection (burst effect)**.** The absolute bioavailability is estimated around 56.8%. The mean residence time of 15.0 ± 1.6 days and the apparent half-life of 5.0 ± 2.3 days, confirm the prolonged release of the product.

After a single administration in acromegaly patients, a comparable pharmacokinetic profile is observed and the levels of growth hormone and IGF-1 are significantly reduced for a period of about 14 days. With repeated administration over several months, there is no evidence of accumulation of lanreotide.

CLINICAL TRIALS

In acromegaly, nine clinical trials were conducted with Somatuline LA in a total of 374 patients. All studies were open label for periods up to 12-18 months and three were multicentre. The principal entry criteria were raised GH and IGF-1 levels without any upper limit. The results were obtained with a treatment regime of one injection of 30mg lanreotide every 14 days with the option of adjusting the dosage interval according to the clinical or biochemical response.

A global view of the clinical trials indicated that lanreotide was effective in ameliorating both the objective and subjective variables of acromegaly, not controlled by surgery. In the long term studies, Somatuline LA treatment reduced GH level over time to < 5.0 ng/mL in up to 89% patients and to < 2.5 ng/mL in up to 74% of patients. In the long term pivotal studies, Somatuline LA treatment normalised IGF-1 levels in up to 55% of patients and both GH levels (GH < 2.5 ng/mL) and IGF-1 levels over the treatment period in 47% of patients.

In all studies the three month data confirmed the maintenance of the relevant clinical and biochemical response and results for the 12-18 month follow-up showed not only a maintenance of efficacy but further improvements were noted in some individual patient responders. There were a number of complete non-responders presumably related to tumours not expressing SSTR2 receptors.

No adequate and well-controlled clinical trials directly comparing Somatuline LA to depot octreotide in the treatment of acromegaly are available. Results from a comparative study (52030 ST 8013) between Somatuline LA and octreotide immediate release (injected subcutaneously three times a day) are presented below. However, in comparing the results with the two products, it should be noted that the study design resulted in GH / IGF-1 levels being measured immediately post-dose for octreotide (peak drug concentration) but immediately prior to the next dose for Somatuline LA (minimum lanreotide concentration). This sampling time difference may explain the apparent greater GH /IGF-1 reduction particularly at the earlier time point.

IGF levels should be considered with great care due to the large numbers of missing data points at week 12 and 24 and thus the relatively small sizes and changing composition of the samples.

Comparative clinical study (52030ST8013) of Somatuline LA and octreotide immediate release in acromegaly GH (ng/mL), levels at day 0, week 12 and week 24 by group for patients fulfilling the inclusion criteria

	Day 0		***Week 12***		***Week 24***	
	Lanreotide (n=20)	*Octreotide (n=17)*	*Lanreotide (n=20)*	*Octreotide (n=17)*	*Lanreotide (n=20)*	*Octreotide (n=17)*
25th % patients	*6.6*	*6.8*	*4.1*	*1.6*	*2.9*	*0.7*
median	*10.5*	*9.5*	*5.7*	*2.7*	*5.0*	*3.5*
75th % patients	*22.5*	*13.5*	*32.3*	*9.3*	*8.7*	*7.4*

Comparative clinical study (52030ST8013) of Somatuline LA and octreotide immediate release in acromegaly IGF-1 (μU/L), levels at day 0, week 12 and week 24 by group for patients fulfilling the inclusion criteria

	Day 0		***Week 12***		***Week 24***	
	Lanreotide (n=18)	*Octreotide (n=12)*	*Lanreotide (n=16)*	*Octreotide (n=13)*	*Lanreotide (n=13)*	*Octreotide (n=11)*
25th % patients	*2.8*	*2.1*	*1.1*	*0.8*	*1.3*	*0.7*
median	*3.6*	*3.0*	*2.1*	*1.1*	*3.1*	*1.3*
75th % patients	*6.8*	*4.0*	*3.6*	*1.7*	*7.2*	*3.0*

INDICATIONS

Somatuline LA 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.

CONTRA-INDICATIONS

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

PRECAUTIONS

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and its analogues, inhibit secretion of insulin and glucagon. Hence, diabetic patients treated with Somatuline LA may experience hypoglycaemia or hyperglycaemia. Blood glucose levels should be monitored when lanreotide therapy is initiated, or when 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. If gallstones do occur, they are generally asymptomatic. Symptomatic stones should be treated as medically indicated.

In patients with hepatic/renal dysfunction, kidney and liver function should be regularly monitored and the dose interval adjusted if necessary. (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.

Effect on fertility

This drug may produce fetal 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 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 Pregnancy (Category C)

Six pregnancies and one suspected pregnancy, have been reported in patients who were being treated with Somatuline LA. 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 data.

Use In Lactation
It is not known whether lanreotide in 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 Contra-indications).

Paediatric Use
As there is no experience of the use of the product in children, the use of Somatuline LA 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.

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, $\leq$ 20) and at 0.1 mg/kg/day in rats (relative exposure, $\leq$ 2). Injection site tumours (fibroma, fibrosarcoma and/or malignant fibrous histiocytoma) were increased in incidence at higher doses (relative exposure, $\geq$ 31 in mice and $\geq$ 3 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.

INTERACTIONS WITH OTHER MEDICINES
The gastrointestinal effects of Somatuline LA may reduce the intestinal absorption of co-administered drugs. As with other somatostatin analogues, Somatuline LA 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 analogue 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.

Effect on Ability to Drive and Use Machines

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

ADVERSE EFFECTS

The adverse effects most commonly reported by patients taking Somatuline LA in clinical trials are gastrointestinal disorders and cholelithiasis.

Undesirable effects reported by patients suffering from acromegaly and treated with Somatuline Autogel or the microparticle formulation Somatuline LA 30mg in clinical trials (almost 600 patients) 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).

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100).**
Metabolism and nutrition disorders		Hypoglycaemia	Diabetes mellitus aggravated, hyperglycaemia
Psychiatric disorders			Insomnia
Nervous system		Dizziness, headache	
Cardiac disorders		Sinus bradycardia	
Vascular disorders			Hot flush
Gastrointestinal disorders	Diarrhoea, loose stools, abdominal pain	Nausea, vomiting, dyspepsia, flatulence, abdominal distension, abdominal discomfort, constipation	Faeces coloured
Hepatobiliary disorders	Cholelithiasis	Biliary dilatation	
Skin and subcutaneous tissue disorders		Alopecia, hypotrichosis	
General disorders and administration site conditions		Fatigue, injection site reactions (pain, mass, induration, nodule, pruritus)	Asthenia
Investigations		ALT increased, AST abnormal, ALT abnormal, blood bilirubin increased, blood glucose increased, glycosylated haemoglobin increased, weight decreased	AST increased, blood alkaline phosphatase increased, blood bilirubin abnormal , blood sodium decreased

Post-marketing safety experience

Gastrointestinal disorders: Unknown: Steatorrhea

Hepatobiliary disorders: Unknown: Cholecystitis

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

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

DOSAGE AND ADMINISTRATION

Initially, one intramuscular injection should be given every 14 days. The frequency of subsequent injections may be varied in accordance with the individual patient's response (as judged by a reduction in GH and/or IGF-1 levels,) such that injections can be given every 7 to 10 days as necessary. No dose modification is required in elderly patients.

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. 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

Pharmaceutical Precautions

Incompatibilities

Somatuline LA must be made up immediately prior to use, using only the solution supplied in the package.

Instructions for use/handling

Somatuline LA must be made up in the supplied solution immediately before injection, by shaking the vial, gently, 20 to 30 times, in order to obtain a homogenous suspension with a milky appearance. This must not be mixed with other medications.

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

OVERDOSAGE

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. In case of overdose, contact Poisons Advisory Centre on 131126 for advice on management. One spontaneous report of a suspected accidental overage of Somatuline LA was reported in a 52 year-old patient receiving 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, 1 week after the last dose.

PRESENTATION & STORAGE CONDITIONS

Type I, clear, slightly tinted, glass vial containing sterile Somatuline LA. Each vial contains 40mg lanreotide, however only 30 mg is available for delivery to the patient, due to losses of the active ingredient during sterilisation, resuspension and administration. Box of 1 vial, 1 ampoule of 0.8% mannitol in 2 mL water for injection (suspension vehicle), 2 needles and 1 syringe.

Shelf-life: 2 years

Special precautions for storage: Store at a temperature between +2°C and 8°C (in the refrigerator), do not freeze.

MANUFACTURER

Ipsen Pharma Biotech
Parc d'Activités du Plateau de Signes
CD No. 402 83870 Signes FRANCE

NAME AND ADDRESS OF THE SPONSOR

Ipsen Pty Ltd
Level 2, Building 4
Brandon Office Park
540 Springvale Road
Glen Waverley 3150

POISON SCHEDULE OF THE MEDICINE: S4

AUST R No: 79153 Somatuline LA 30mg

Date of first inclusion in ARTG: 11th October 2001
Date of most recent amendment: 16th December 2014