Physician's Prescribing Information

1 TRADE NAME OF THE MEDICINAL PRODUCT

SOMATULINE P.R. 30 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lanreotide acetate, expressed as lanreotide ..... 0.03000 g *

For one vial

* Taking into account the characteristics of the pharmaceutical form, each vial contains a quantity of lanreotide acetate corresponding to 0.04 g of lanreotide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for prolonged release suspension for injection (I. M.).

The powder is made of lyophilised microspheres.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acromegaly (when the treatment of growth hormone is not normalized after surgery and/or radiotherapy).

Treatment of clinical symptoms of carcinoid tumours (after a test injection).

Treatment of primary thyrotropic adenomas responsible for hyperthyroidism as a preparation for /or as a complement to surgery and/or radiotherapy, or where these therapies are unsuitable.

4.2 Posology and method of administration

The treatment should be adjusted to each patient in a specialised unit.

Posology

Taking into account the variability of the sensitivity of the tumours to somatostatin analogues, it is recommended to start treatment with a test injection, in order to assess the quality of the response (GH secretion, symptoms related to the carcinoid tumour, tumoral secretions...).

If no response to the first test injection is seen, the treatment should be reviewed.

<u>In acromegaly</u>

The frequency of administration of the prolonged release form can initially be set to one intramuscular injection every 14 days. In case of an insufficient response, judged by the levels of growth hormone and IGF-1 (measured prior to the next injection), the frequency of injection may be increased to 1 every 10 days.

In carcinoid tumours

The frequency of administration of the prolonged release form can initially be set to one intramuscular injection every 14 days. In case of an insufficient response, judged by clinical symptoms (flushes, soft stools), the frequency of injection may be increased to 1 every 10 days.

In primary thyrotropic adenomas responsible for hyperthyroidism :

The frequency of administration of the prolonged release form should initially be set to one intramuscular injection every 14 days. In case of an insufficient response, as judged by the levels of thyroid hormone and TSH, the frequency of injection may be increased to 1 every 10 days.

Renal and/or hepatic impairment
In patients with impaired renal or hepatic function, no dosage adjustment is necessary (see section 5.2).

Elderly patients
In elderly patients, no dosage adjustment is necessary (see section 5.2).

Paediatric population
SOMATULINE PR 30 mg is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Method of administration
Somatuline P.R. 30 mg is administered by intra muscular injection in the superior external quadrant of the buttock.
The intramuscular injection site should be alternated between left and right sides.

For instructions on dilution of the product before administration, instructions for use, handling and disposal of the product, see section 6.6.

4.3 Contra-indications

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

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4.4 Special warnings and special precautions for use

▪ Lanreotide may reduce gallbladder motility and lead to gallstone formation. Therefore patients may need to be monitored periodically. It is advised, during prolonged treatment, to perform before treatment and every 6 months, an echography of the gallbladder (see section 4.8).

▪ Pharmacological studies in animals and humans show that lanreotide, like somatostatin and other somatostatin analogues, inhibits 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. Any antidiabetic treatment should be adjusted accordingly. In insulin-treated diabetic patients, the insulin doses will initially be reduced by 25%, then adapted to the

blood glucose level, which must be carefully controlled in these patients as soon as treatment begins.

▪ 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 acromegalic patients and patients presenting with primitive thyrotropic adenomas, use of lanreotide is not exempt from the monitoring of the volume of the pituitary tumour.

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

▪ The appearance of a significant and lasting increase of steatorrhoea justifies the complementary prescription of pancreatic extracts.

4.5 Interaction with other medicaments and other forms of interaction

Associations requiring precautions for use

Cyclosporine (oral use) : decrease in cyclosporine blood levels (decrease in the intestinal cyclosporine absorption). Increase the cyclosporine dose under the control of circulating blood levels and reduction of doses after stopping lanreotide treatment.

Insulin, glitazones, repaglinide, sulphonylureas : risk of hypoglycaemia or hyperglycaemia : decrease in the needs of antidiabetic treatment following decrease or increase in endogen glucagon secretion. The glycaemic self monitoring must be reinforced and the posology of antidiabetic treatment during treatment by lanreotide should be adapted as required.

▪ Concomitant administration of bradycardia inducing drugs (e.g. 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 (see section 4.4).

▪ 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 lanreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine) should therefore be used with caution.

Other information

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

Studies in animals showed no evidence of teratogenic effects associated with lanreotide during organogenesis.

The number of pregnancies exposed to lanreotide is very limited. Therefore, lanreotide should be administered to pregnant women only if clearly needed.

Lactation

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.

Fertility

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.

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 PR 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 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 other 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)
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 flushes*	
Gastrointestinal disorders	Diarrhoea, loose stools*, abdominal pain	Nausea, vomiting, constipation, flatulence, abdominal distension,	Faeces discoloured*	Pancreatitis

		abdominal discomfort, dyspepsia, steatorrhoea**		
Hepatobiliary disorders	Cholelithiasis	Biliary dilatation*		
Musculoskeletal and connective tissue disorders		Musculoskeletal 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 suspected adverse reaction after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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.

Its marked selectivity for the secretion of growth hormone compared to that of insulin, makes this a product suited to the treatment of acromegaly.

By inhibiting the synthesis of thyroid stimulating hormone (TSH), lanreotide normalised also the thyroid function on patient with thyrotropin-secreting adenomas.

Furthermore, the inhibitory action of lanreotide on intestinal exocrine secretion, digestive hormones and cellular proliferation mechanisms is particularly interesting for its application in the treatment of the symptoms 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 hydroelectrolytic secretion (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.

A randomised, placebo controlled study has investigated the effects of lanreotide PR 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 lanreotide PR 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]).

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 were 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 PR 30mg 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 micro particles 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 PR 30mg 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 are 2.2 ± 0.7 and 2.8 ± 0.8 ng/mL respectively. 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 modify the starting dose in patients with renal or hepatic impairment, as lanreotide serum concentrations in these populations are expected to be maintained within the range of serum concentrations safely tolerated in healthy subjects.

Elderly patients

Elderly subjects show an increase in half-life and mean residence time compared with healthy young subjects. It is not necessary to modify the starting dose in elderly patients, as lanreotide serum concentrations in this population are expected to be maintained 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 microspheres is completed in 45 – 60 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Copolymers (lactide-glycolide and lactic-glycolic), mannitol, carmellose sodium, polysorbate 80

Solvent: Mannitol, water for injection

6.2 Incompatibilities

The microspheres must be reconstituted immediately prior to use, using only the solution supplied in the package.

6.3 Shelf-life

2 years.

After opening: the product should be used immediately after reconstitution.

6.4 Special precautions for storage

To be stored at a temperature between + 2° C and + 8° C.

6.5 Nature and contents of container

Powder in a vial (glass) and 2 ml of solvent in an ampoule (glass).

6.6 Instructions for use/handling

The reconstitution of the powder in the specific solvent must be performed immediately before injection, by shaking the vial gently 20 to 30 times, until an homogenous suspension with a milky appearance is obtained.

This must not be mixed with other medications.

7 MANUFACTURER

IPSEN PHARMA, FRANCE

8 IMPORTER ANF LICENSE HOLDER

Medison Pharma Ltd. POB 7090, Petach Tikva 49170

9 REGISTRATION NUMBER

117-93-29911-00