1 NAME OF THE MEDICINAL PRODUCT

Somatuline® Autogel® prolonged-release solution for injection in a pre-filled syringe 120 mg
Somatuline® Autogel® prolonged-release solution for injection in a pre-filled syringe 90 mg
Somatuline® Autogel® prolonged-release solution for injection in a pre-filled syringe 60 mg

2 QUALITATIVE AND QUANTITAVE COMPOSITION

Lanreotide 60 mg, 90 mg and 120 mg (presented as lanreotide acetate)
Each pre-filled syringe contains a supersaturated solution of lanreotide acetate corresponding to 0.246 mg of lanreotide base/mg of solution, which ensures an actual injection dose of 60 mg, 90 mg and 120 mg, respectively.

3 PHARMACEUTICAL FORM

Prolonged-release solution for injection in a pre-filled syringe.
White to pale yellow semi-solid formulation.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the long-term treatment of individuals with acromegaly when the circulating levels of Growth Hormone (GH) and/or Insulin-like Growth Factor-1 (IGF-1) remain abnormal after surgery and/or radiotherapy or in patients who require medical treatment. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalize these values.
For the relief of symptoms associated with acromegaly.
For the reduction of the symptoms associated with carcinoid syndrome.
For the treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease.

4.2 Posology and Method of Administration

Initiation of treatment

Acromegaly
The recommended starting dose is 60 mg to 120 mg administered every 28 days.
For example:

- in patients previously treated with SOMATULINE P.R. 30 mg powder and solvent for prolonged-release suspension for injection (I.M.) every 14 days, the initial dose of Somatuline® Autogel® should be 60 mg every 28 days;
- in patients previously treated with SOMATULINE P.R. 30 mg powder and solvent for prolonged-release suspension for injection (I.M.) every 10 days, the initial dose of Somatuline® Autogel® should be 90 mg every 28 days;
- in patients previously treated with SOMATULINE P.R. 30 mg powder and solvent for prolonged-release suspension for injection (I.M.) every 7 days, the initial dose of Somatuline® Autogel® should be 120 mg every 28 days;

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

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

Adaptation of treatment

The treatment should be adjusted for each patient in a specialised unit.
The dose should be individualised according to the response which is evaluated by monitoring plasma GH and IGF-1 levels and by assessing changes in symptoms.

Acromegaly
It is recommended:

- to reduce the dose when the concentrations are normalised (GH < 1 ng/ml and normalised IGF-1 and/or disappearance of clinical symptoms),
- to maintain the dose when the concentrations of GH are between 2.5 ng/ml and 1 ng/ml,
- to increase the dose when the concentrations of GH are higher than 2.5 ng/ml.

Patients well controlled on a somatostatin analogue can be treated with Somatuline® Autogel® 120 mg every 42 or 56 days.
Long term monitoring of symptoms, GH and IGF-1 levels should be routinely carried out in all patients.

Carcinoid tumours
In case of an insufficient response judged by clinical symptom (reduction in episodes of flushing or diarrhoea), the dose may be increased to 120 mg every 28 days (4 weeks). In case of a sufficient response judged by clinical symptom (reduction in episodes of flushing or diarrhoea), the dose may be decreased to 60 mg every 28 days (4 weeks).

Renal and/or hepatic impairment
In patients with impaired renal or hepatic function, no dosage adjustment is necessary.

Elderly patients
In elderly patients, no dosage adjustment is necessary.

Paediatric population
Somatuline® Autogel® is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Method of Administration
Somatuline® Autogel® is administered by deep subcutaneous injection in the superior external quadrant of the buttock or in the upper outer thigh. The injection is made by healthcare professional. However, for patients who receive a stable dose of Somatuline® Autogel®, the product may be administered either by the patient or by a person around him after appropriate training by a healthcare professional.
In case of self-injection, the injection should be made in the upper outer thigh.

The decision of administration by the patient or another trained person should be taken by the healthcare professional.
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 alternate between the right and left side.

4.3 Contraindications

Hypersensitivity to the active substance, somatostatin or related peptides or to any of the excipients listed in the excipients list.

4.4 Special warnings and 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. 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.
Pharmacological studies in animals and humans showed 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.
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 adenoma, 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.
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.

4.5 Interaction with other medicinal products and other forms of interaction

Cyclosporin (oral route use)
The pharmacological gastrointestinal effects of lanreotide may result in the reduction of the intestinal absorption of coadministered drugs including cyclosporin. Concomitant administration of cyclosporin with lanreotide may decrease the relative bioavailability of ciclosporin and therefore may necessitate the adjustment of ciclosporin dose to maintain therapeutic levels.
Insulin, glitazones, repaglinide, sulphonylureas
Risk of hypoglycaemia or hyperglycaemia: decrease in the needs of anti-diabetic treatment following the 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.

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 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 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
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 (see section 5.3). The potential risk for humans is unknown.
As a precautionary measure, it is preferable to avoid the use of lanreotide during pregnancy.
Breast-feeding
It is not known whether Somatuline® Autogel® is excreted in human milk.
A risk to the newborns/infants cannot be excluded.
Somatuline® Autogel® should not be used during breast-feeding.
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

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® (see section 4.8). If a patient is affected, he/she should not drive or operate machinery.

4.8 Undesirable side effects

Undesirable effects reported by patients suffering from acromegaly and 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); not known (cannot be estimated from the available data).
The most common 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, nodule 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)
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, abdominal discomfort*, dyspepsia, steatorrhoea**	Faeces discoloured*	Pancreatic exocrine insufficiency, pancreatitis
Hepatobiliary disorders	Cholelithiasis	Biliary dilatation*		Cholangitis, cholecystitis
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)		Injection site abscess
Investigations		ALAT increased*, ASAT abnormal*, ALAT abnormal*, blood	ASAT increased*, blood alkaline phosphatase increased*, blood bilirubin	

		bilirubin increased*, blood glucose increased*, glycosylated haemoglobin increased*, weight decreased, pancreatic enzymes decreased**	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

4.9 Overdose
If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Pituitary and hypothalamic hormones and analogues; Somatostatin and analogues.
ATC code: H01C B03
Mechanism of Action:
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.
Lanreotide is more active than natural somatostatin and shows a longer duration of action.
Its marked selectivity for the secretion of growth hormone compared to that of insulin, makes this a product suited to the treatment of acromegaly.
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. Additionally, it decreases the levels of plasma chromogranin A and urinary 5-HIAA (5 Hydroxyindolacetic acid) in patients with GEP-NETs and elevated levels of these tumour markers. Lanreotide 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.

In an open-label study, Somatuline Autogel 120 mg was administered every 28 days for 48 weeks in 90 previously untreated acromegalic patients diagnosed with pituitary macroadenoma.

At week 48, 63% of the patients 63% of the patients showed a clinically relevant reduction in tumour volume of ≥ 20% (which was the primary efficacy endpoint) although statistical significance was not reached (95% CI: 52% – 73%).
The mean percentage reduction of tumour volume was 26.8%, GH levels were below 2.5 μg/L in 77.8% of the patients and IGF-1 levels normalised in 50%. Normalised IGF-1 levels combined with GH levels below 2.5 μg/L were observed in 43.5% of the patients.
Patients reported a relief of acromegaly symptoms such as fatigue (56.5%), excess perspiration (66.1%), arthralgia (59.7%), soft tissue swelling (66.1%) and headache (38.7%).
A reduction in tumour volume and concentrations of GH and IGF-1 was shown from week 12 and was maintained for 48 weeks. The study excluded patients who were expected to require pituitary surgery or radiotherapy during the study period.

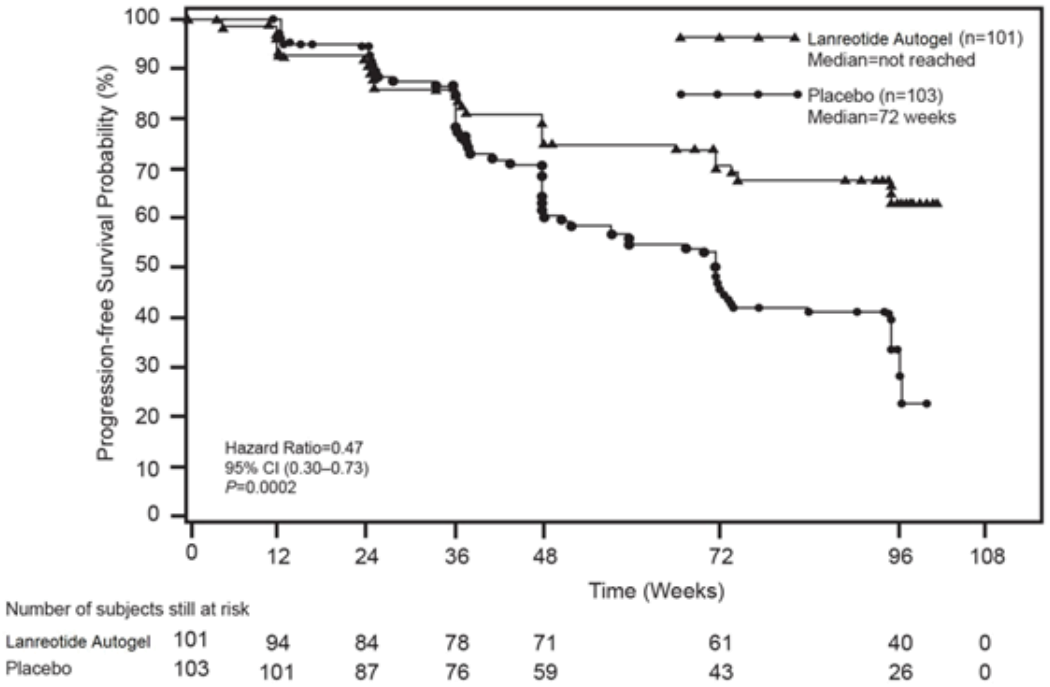
A phase III, 96-week, fixed duration, randomized, double-blind, multi-centre, placebo-controlled trial was conducted in patients with gastroenteropancreatic neuroendocrine tumours to assess the antiproliferative effect of lanreotide.

Patients were randomized 1:1 to receive either Somatuline® Autogel® every 28 days (n=101) or placebo (n=103). 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.
Patients had metastatic and /or locally advanced inoperable disease with histologically confirmed well or moderately well differentiated tumours primarily localized in the pancreas (44.6% patients), midgut (35.8%), hindgut (6.9%) or of other/unknown primary location 12.7%).
69% of patients with GEP-NETs had tumour grade 1 (G1), defined by either a proliferation index Ki67 ≤ 2% (50.5% of the overall patient population) or a mitotic index < 2 mitosis/10 HPF (18.5% of the overall patient population) and 30% of patients with GEP-NETs had tumours in the lower range of grade 2 (G2) (defined by a Ki67 index > 2% – ≤ 10%). Grade was not available in 1% of the patients.
The study excluded patients with G2 GEP-NETs with a higher cellular proliferation index (Ki 67 >10% – ≤ 20%) and G3 GEP neuroendocrine carcinomas (Ki 67 index > 20%).
Overall, 52.5% of the patients had an hepatic tumour load ≤ 10%, 14.5% had an hepatic tumour load > 10 and ≤ 25% and 33% had an hepatic tumour load >25%. 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.

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

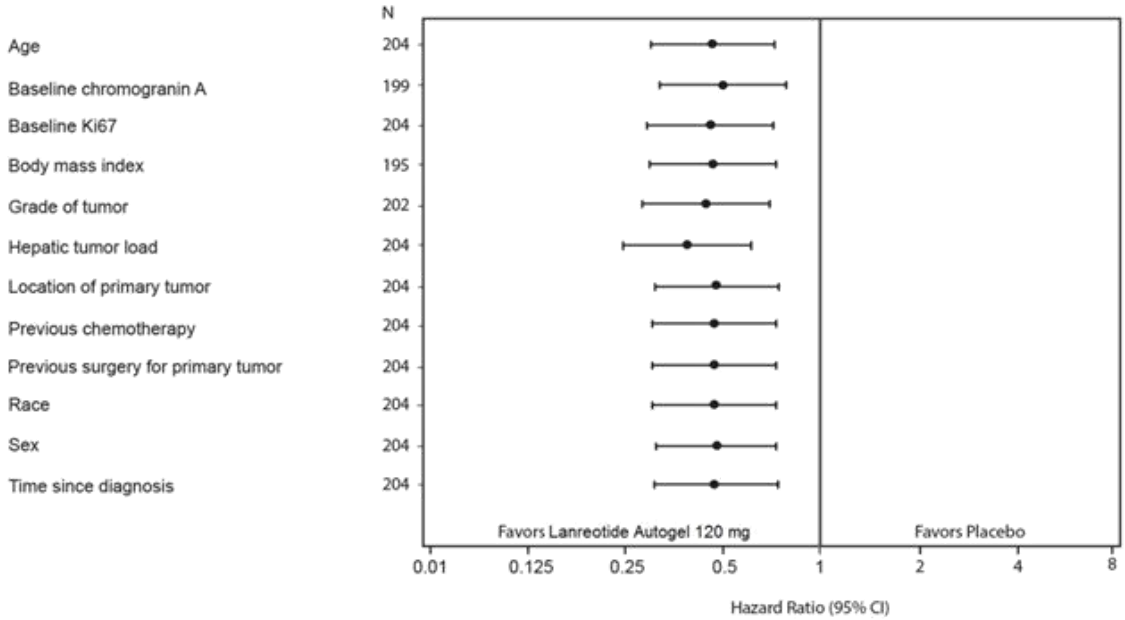
Figure 1: Kaplan-Meier Progression Free Survival Curves



The beneficial effect of lanreotide in reducing the risk of progression or death was consistent regardless of the location of primary tumour, hepatic tumour load, previous chemotherapy, baseline Ki67, tumour grade or other pre-specified characteristics as shown in Figure 2.

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.

Figure 2: Results of the Cox Proportional Hazards Covariates Analysis of PFS



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.

Crossover from placebo to open-label Somatuline® Autogel®, in the extension study, occurred in 45.6% (47/103) of the patients.

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.

After deep subcutaneous administration of Somatuline® Autogel® 60, 90 and 120 mg to healthy volunteers, lanreotide concentrations increase to achieve average maximum serum concentrations of 4.25, 8.39 and 6.79 ng/ml. These values of C_{max} are achieved during the first day after the administration at 8, 12 and 7 hours (median values). From the peak serum levels of lanreotide concentrations decrease slowly following a first order kinetics with a terminal elimination half-life of 23.3, 27.4 and 30.1 days respectively and 4 weeks after the administration mean lanreotide serum levels were 0.9, 1.11 and 1.69 ng/ml respectively. Absolute bioavailability was 73.4, 69.0 and 78.4%.

After deep subcutaneous administration of Somatuline® Autogel® 60, 90 and 120 mg to acromegalic patients, lanreotide concentrations increase to achieve average maximum serum concentrations of 1.6, 3.5 and 3.1 ng/ml. These values of C_{max} are achieved during the first day after the administration at 6, 6 and 24 hours. From the peak serum levels of lanreotide concentrations decrease slowly following first order kinetics and 4 weeks after the administration mean lanreotide serum levels were 0.7, 1.0 and 1.4 ng/ml, respectively.

Steady state serum levels of lanreotide were reached, on average, after 4 injections every 4 weeks. After repeated dose administration every 4 weeks the average values of C_{max} at steady state were 3.8, 5.7 and 7.7 ng/ml for 60, 90 and 120 mg respectively, the average C_{min} values obtained being 1.8, 2.5 and 3.8 ng/ml. The peak through fluctuation index was moderate ranging from 81 to 108%.

Linear pharmacokinetic release profiles were observed after deep subcutaneous administration of Somatuline® Autogel® 60, 90 and 120 mg in acromegalic patients.

In a population PK analysis in 290 GEP-NET patients receiving Somatuline® Autogel® 120mg, 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 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 terminal half-life was 49.8 ± 28.0 days.

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.

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® 120 mg. GEP-NET patients with severely impaired renal function were not studied. No GEP-NET patients with hepatic impairment (as per Child-Pugh score) were studied.

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

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use
In carcinogenic bioassay 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.
Lanreotide was not teratogenic in rats and rabbits. Embryo/foetal toxicity was observed in rats (increased pre-implantation loss) and in rabbits (increased post-implantation loss). Reproductive studies in pregnant rats given 30 mg/kg by subcutaneous injection every 2 weeks (five times the human dose, based on body surface area comparisons) resulted in decreased embryo/foetal survival. Studies in pregnant rabbits given subcutaneous injections of 0.45 mg/kg/day (two times the human therapeutic exposures at the maximum recommended dose of 120 mg, based on comparisons of relative body surface area) shows decreased foetal survival and increased foetal skeletal/soft tissue abnormalities.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for injections, acetic acid (for pH adjustment).

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
3 years.
After opening the protective laminated pouch, the product should be administered immediately.

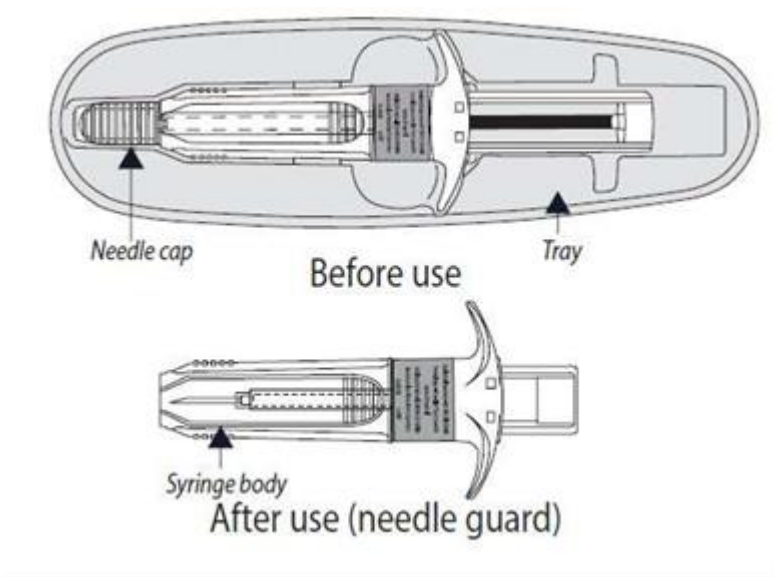
6.4 Special precautions for storage
Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light.
Once removed from the refrigerator, product left in its sealed pouch may be returned to the refrigerator (the number of temperature excursions must not exceed three times) 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
Somatuline® Autogel® is supplied in a pre-filled syringe (polypropylene) fitted with an automatic safety system with a plunger stopper (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 a cardboard box.
Box of one 0.5 ml pre-filled syringe with an attached needle (1.2 mm × 20 mm).

7 INSTRUCTIONS FOR USE AND HANDLING

The Somatuline® Autogel® 60 mg, 90 mg and 120 mg prolonged-release solution for injection in a pre-filled syringe is a ready-for use supersaturated lanreotide solution that forms a whitish, translucent autogel.
For immediate and single use following first opening.
It is important that the injection of the product is performed exactly according to the instruction in the package leaflet.
Do not use if the laminated pouch is damaged or opened.
Any unused product or waste material should be disposed of in accordance with local requirements.
The following instructions explain how to inject Somatuline® Autogel®.
Somatuline® Autogel® is supplied in a ready to use pre-filled syringe fitted with an automatic safety system. The needle will retract automatically following the full administration of the product, to prevent needle stick injury.



1. Remove Somatuline® Autogel® from the refrigerator 30 minutes prior to administration. Injection of cold medication may be painful. Keep laminated pouch sealed until just prior to injection.

2. Attention: Before opening the pouch, check that it is intact and that the medication has not expired.

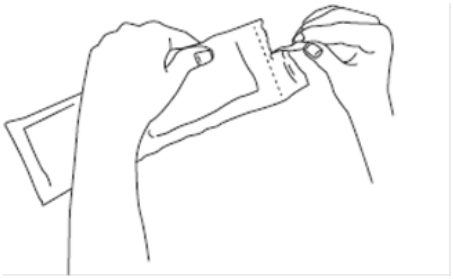
<u>Do not use the pre-filled syringe:</u>

- If you drop or damage the pre-filled syringe or if the pre-filled syringe or pouch appear damaged in any way;
- If the product has expired; the expiry date is printed on the outer carton and the pouch.

If any of the above apply, you should contact your doctor or pharmacist.

3. Wash hands with soap.

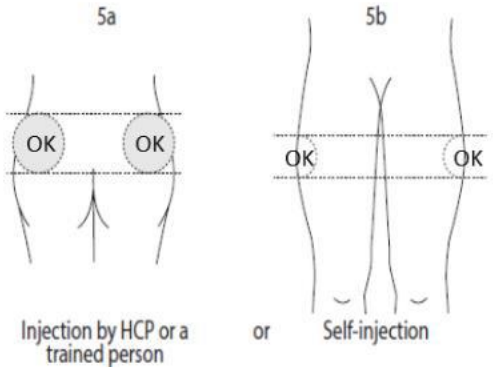
4. Tear-open the pouch along the dotted line and take out the pre-filled syringe. The content of the pre-filled syringe is a semi-solid phase having a gel-like appearance, with viscous characteristics and a colour varying from white to pale yellow. The supersaturated solution can also contain micro bubbles that can clear up during injection. These differences are normal and do not interfere with the quality of the product.
   After opening the protective laminated pouch, the product should be administered immediately.



5. Select an injection site:

5a. If a healthcare professional (HCP) or someone else like a trained family member or friend is doing the injection: use the superior external (upper, outer) quadrant of the buttock (for injection. by healthcare professional (HCP) or someone else like a trained family member or friend),

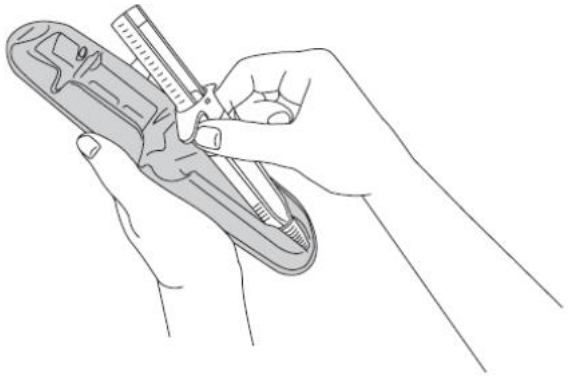
5b. If you are injecting yourself: use the upper outer part of your thigh. (if you will be injecting yourself).



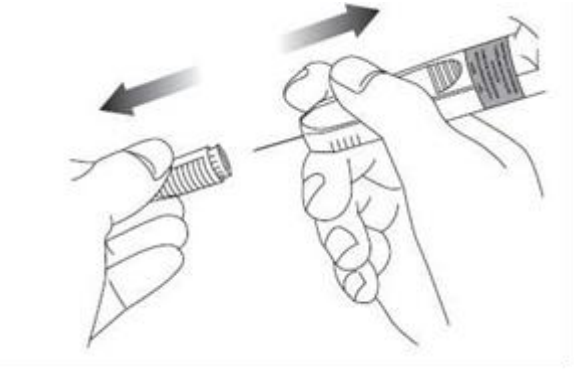
Alternate the injection site between the right and left side each time you receive an injection of Somatuline® Autogel® Avoid areas with moles, scar tissues, reddened skin, or skin that feels bumpy.

6. Clean the injection.

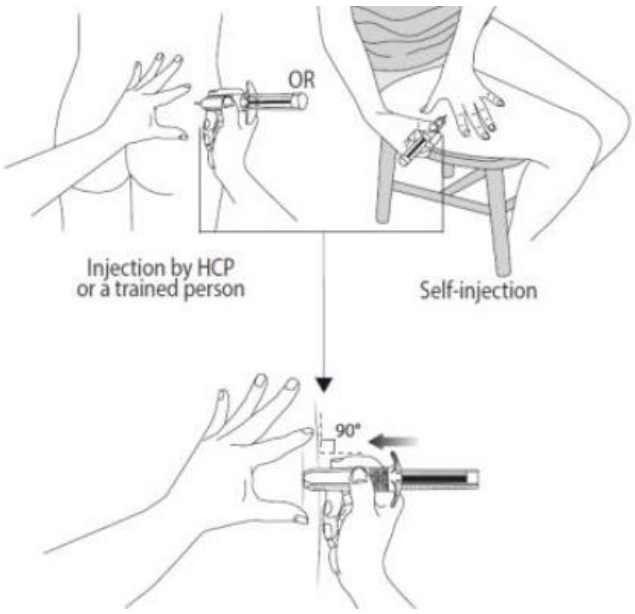
7. Before injecting, remove the pre-filled syringe from its tray. Discard the tray.



8. Remove the needle cap by pulling off and discarding it.

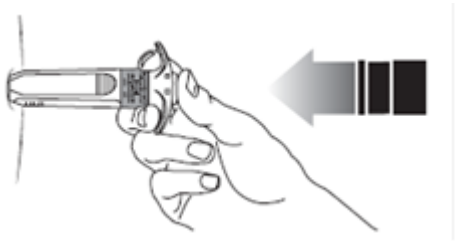


9. Flatten injection area using the thumb and index finger of the hand not holding the pre-filled syringe to stretch the skin. **Do not pinch the skin**. Use a strong, straight dart-like motion to **quickly insert** the needle perpendicular to the skin (90 degree angle), all the way into the skin. It is very important that you insert the needle **completely**. You should not see any needle once it is fully inserted.
   Do not aspirate (do not draw back).

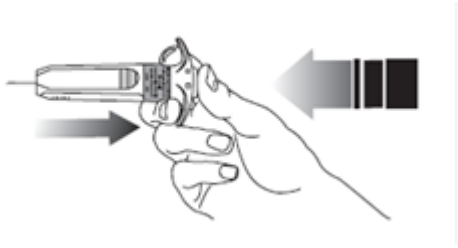


10. Release inject site that has been flattened by you hand. Push plunger with **steady very firm pressure**. The medication is thicker and harder to push than you might expect. Typically, 20 seconds are needed. Inject the full dose and give a final push to make sure you cannot depress it any further.

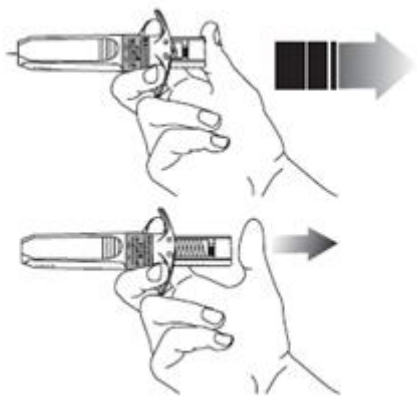
Note: maintain pressure on the plunger with your thumb to avoid activation of the automatic safety system.



11. Without releasing the pressure on the plunger, withdraw the needle from the injection site.



12. Then release pressure on the plunger. The needle will automatically retract into the needle guard where it will be locked permanently.



13. Apply gentle pressure to the injection site with a dry cotton ball or sterile gauze to prevent any bleeding. Do not rub or massage the injection site after administration.

14. Dispose of the used syringe as instructed by your doctor or healthcare provider. Do not dispose of the device in your general household rubbish.

8 NAME AND ADDRESS OF MANUFACTURER

Ipsen Pharma Biotech
Chemin Departmental No. 402 – 83870 Signes – France

9 DATE OF REVISION

May 2024