PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SOMATULINE® AUTOGEL® 60, solution for injection.

SOMATULINE® AUTOGEL® 90, solution for injection.

SOMATULINE® AUTOGEL® 120, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SOMATULINE AUTOGEL 60: Each pre-filled syringe contains lanreotide acetate equivalent to 60 mg lanreotide.

SOMATULINE AUTOGEL 90: Each pre-filled syringe contains lanreotide acetate equivalent to 90 mg lanreotide.

SOMATULINE AUTOGEL 120: Each pre-filled syringe contains lanreotide acetate equivalent to 120 mg lanreotide.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

White to pale yellow semi-solid phase in a pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOMATULINE AUTOGEL is indicated for:

- Treatment of acromegaly when secretions of growth hormone (GH) and insulin-like growth

factor 1 (IGF-1) remain abnormal after surgery and/or radiotherapy.

- Treatment of the clinical symptoms associated with acromegaly.
- Treatment of the symptoms related to neuroendocrine tumours (NETs) with characteristics of the carcinoid syndrome.
- Treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adult patients with unresectable locally advanced or metastatic disease, to improve progression-free survival.

4.2 Posology and method of administration

Posology:

Acromegaly

The recommended starting dose is 90 mg administered every 28 days for 3 months.

Thereafter, 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 growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels and by assessing changes in symptoms.

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 1 ng/mL and 2,5 ng/mL,
- to increase the dose when the concentrations of GH are higher than 2,5 ng/mL.

Patients well controlled on a first generation somatostatin analogue can be treated with a maximum dose of SOMATULINE AUTOGEL 120 mg every 42 or 56 days.

Long-term monitoring of symptoms, GH and IGF-1 levels should be undertaken as clinically indicated.

Treatment of symptoms related to neuroendocrine tumours (NETs) with characteristics of the carcinoid syndrome:

The recommended starting dose is 90 mg administered every 28 days during 2 months.

The dose should be adjusted according to the degree of symptomatic relief obtained.
In case of an insufficient response judged by clinical symptoms (flushes and soft stools), the dose may be increased to 120 mg every 28 days (4 weeks).
In case of a sufficient response judged by clinical symptoms (flushes and soft stools), the dose may be decreased to 60 mg every 28 days (4 weeks).

Treatment of gastroenteropancreatic neuroendocrine tumours in adult patients with unresectable locally advanced or metastatic disease:

The recommended dose is one injection of SOMATULINE AUTOGEL 120 mg administered every 28 days. The treatment with SOMATULINE AUTOGEL should be continued for as long as effective for tumour control.

Special populations

Hepatic impairment

The starting dose of SOMATULINE AUTOGEL in patients with moderate to severe hepatic impairment should be 60 mg via the deep subcutaneous route, at 4-week intervals for 3 months, followed by a dose adjustment as described above (see section 4.4 and section 4.2).

Renal impairment

In GEP-NET patients with mild or moderate renal impairment the SOMATULINE AUTOGEL starting dose is 120 mg via the deep subcutaneous route, at 4-week intervals.
In GEP-NET patients with severe renal impairment and acromegaly patients with moderate to severe renal impairment, the starting dose should be 60 mg via the deep subcutaneous route, at 4-week intervals for 3 months, followed by a dose adjustment as described above. The SOMATULINE AUTOGEL dose could be increased from 60 mg to 120 mg before the 3-month period if the treatment is well-tolerated.

Paediatric population

Currently there is no experience of administration of SOMATULINE AUTOGEL in children and adolescents, therefore use of SOMATULINE AUTOGEL in children and adolescents cannot be recommended.

Method of administration

Remove SOMATULINE AUTOGEL from the refrigerator 30 minutes prior to administration, but keep the pouch sealed during this time. Refer to section 6.3 for more information.

SOMATULINE AUTOGEL should be injected via the deep subcutaneous route in the superior external quadrant of the buttock or in the upper outer thigh. The injection should be administered by a healthcare professional.

For patients on a stable dose regimen of SOMATULINE AUTOGEL, the product may be administered either by the patient or by another trained person after appropriate training by a healthcare professional.
In case of self-injection, the injection should be given in the upper outer thigh.

The decision of administration by the patient or by another trained person, should be taken by a 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.
Each syringe is intended for single use only.

4.3 Contraindications

- Hypersensitivity to lanreotide, to somatostatins or related peptides, or to any of the excipients in SOMATULINE AUTOGEL (see section 6.1).

- Complicated, untreated lithiasis of the bile ducts.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Renal impairment:

Safety of SOMATULINE AUTOGEL has not been demonstrated in patients with renal impairment in acromegaly or in patients with severe renal impairment in GEP-NET disease.

Subjects with severe renal impairment showed an approximately 2-fold decrease in total clearance of SOMATULINE AUTOGEL, with a consequent increase in half-life and AUC.
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.
See section 5.2.

Hepatic impairment:

Safety of SOMATULINE AUTOGEL has not been demonstrated in patients with hepatic impairment in acromegaly and GEP-NET disease.
Subjects with hepatic impairment have shown an increase in volume of distribution and mean residence time. In subjects with moderate to severe hepatic impairment, a reduction in clearance was observed (30 %).
See section 5.2.

Blood glucose levels:

Pharmacological studies in humans show that SOMATULINE AUTOGEL may produce a transient inhibition of the secretion of insulin and glucagon. Hence, patients treated with SOMATULINE AUTOGEL may experience hypoglycaemia or hyperglycaemia. Blood glucose levels should be monitored when SOMATULINE AUTOGEL treatment is initiated, or when the dose is altered and any antidiabetic treatment should be adjusted accordingly.

Cholelithiasis and complications of cholelithiasis:

SOMATULINE AUTOGEL may reduce gallbladder motility and lead to gallstone formation. Thus, gallbladder echography is advisable in all patients who have not undergone cholecystectomy, and this both at the start and frequently during the course of the treatment. The incidence of cholelithiasis and sludge inside the gallbladder increases with the dose and duration of treatment and was commonly observed in clinical studies. Gallstones may be asymptomatic. 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 SOMATULINE AUTOGEL and treat appropriately.

Thyroid function:

Slight decreases in thyroid function have been seen during treatment with SOMATULINE AUTOGEL in acromegalic patients, though clinical hypothyroidism is rare. Thyroid function tests are recommended where clinically indicated.

Cardiac disorders:

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

Other:

In acromegalic patients, use of SOMATULINE AUTOGEL is not exempt from the monitoring of the volume of the pituitary tumour.

4.5 Interaction with other medicines and other forms of interaction

Ciclosporin:

The pharmacological gastrointestinal effects of SOMATULINE AUTOGEL may result in a reduction of the intestinal absorption of co-administered medicines including ciclosporin. Concomitant administration of SOMATULINE AUTOGEL injection with ciclosporin may decrease the relative bioavailability of ciclosporin and therefore may necessitate the adjustment of ciclosporin dose to maintain therapeutic levels. Blood concentration of ciclosporin should therefore be monitored during treatment with SOMATULINE AUTOGEL and after treatment has been withdrawn.

Insulin, glitazones, repaglinide and sulphonylureas:

Risk of hypoglycaemia or hyperglycaemia: decrease in antidiabetic treatment needs following decrease or increase in endogenous glucagon secretion.

Patients must be informed:

- of the risk of hypoglycaemia or hyperglycaemia,
- that the glycaemic and urinary self-monitoring must be reinforced, and
- that the dose of antidiabetic treatment during treatment with SOMATULINE AUTOGEL should be adjusted 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 medicines (e.g. beta blockers) may have an additive effect on the slight reduction of heart rate associated with SOMATULINE AUTOGEL. 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 SOMATULINE AUTOGEL may have this effect, other medicines mainly metabolised by CYP3A4 and which have a low therapeutic index (e.g. quinidine) should therefore be used with caution.

Interactions with highly plasma bound medicines are unlikely in view of the moderate binding of SOMATULINE AUTOGEL to serum proteins (78 % mean serum binding).

4.6 Fertility, pregnancy and lactation

SOMATULINE AUTOGEL is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

Studies in animals have shown reproductive toxicity but no evidence of teratogenic effects. The potential risk for humans is unknown.

In clinical practice, no relevant information is available to evaluate whether SOMATULINE AUTOGEL causes malformations or fetotoxicity. However, in view of its pharmacological activity (growth hormone antagonism), SOMATULINE AUTOGEL is contraindicated in pregnant women.

Breastfeeding

SOMATULINE AUTOGEL is contraindicated in women breastfeeding their infants (see section 4.3). Women on treatment with SOMATULINE AUTOGEL should not breastfeed their infants.

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, lethargy and fatigue have been reported with SOMATULINE AUTOGEL. If a patient is affected, he/she should not drive or operate machinery.

4.8 Undesirable effects

The side effects observed in clinical trials with SOMATULINE AUTOGEL are predominantly

gastrointestinal. In clinical trials of SOMATULINE AUTOGEL in acromegalic patients, 80 % of patients experienced at least one side effect. More than 50 % of these side effects were classified as gastrointestinal system disorders.

The most commonly reported adverse reactions following treatment with SOMATULINE AUTOGEL 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).

Side effects are listed under the corresponding system organ class.

The frequencies of the side effects are given according to the following convention:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000).

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1 000, < 1/100)**
Metabolism and nutrition disorders		decreased appetite**, hypoglycaemia, hyperglycaemia, diabetes mellitus	abnormal glucose tolerance
Psychiatric disorders			insomnia
Nervous system disorders		lethargy**, headache, dizziness	
Cardiac disorders		sinus bradycardia	
Vascular disorders			hot flushes
Gastrointestinal disorders	diarrhoea, loose stools, abdominal pain, nausea	constipation, flatulence, abdominal distention, abdominal discomfort, dyspepsia, vomiting,	tenesmus, discoloured faeces

		steatorrhoea**	
Hepatobiliary disorders	cholelithiasis, gallbladder sludge	biliary dilatation	
Skin and subcutaneous tissue disorders		alopecia, hypotrichosis	
Musculoskeletal and connective tissue disorders		musculoskeletal pain**, myalgia**	
General disorders and administration site conditions		fatigue, asthenia, injection site reactions (pain, redness, mass, induration, nodule, pruritus)	skin nodules, somnolence, leg pain, decreased libido, increased sweating, malaise
Investigations		decreased pancreatic enzymes**, increased alanine aminotransferase (ALAT), abnormal ASAT, abnormal ALAT, increased blood bilirubin, increased blood glucose, increased glycosylated haemoglobin, decreased weight	increased aspartate aminotransferase (ASAT), increased blood alkaline phosphatase, abnormal blood bilirubin, decreased blood sodium

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

POST-MARKETING SAFETY DATA

Frequencies from post-marketing surveillance are not known (cannot be estimated from available data).

System organ class	Adverse drug reaction
Infections and infestations	injection site abscess
Gastrointestinal disorders	pancreatitis
Hepatobiliary disorders	cholecystitis, cholangitis
Immune system disorders	allergic reactions (including angioedema, anaphylaxis, hypersensitivity)

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of SOMATULINE AUTOGEL is important. It allows continued monitoring of the benefit/risk balance of SOMATULINE AUTOGEL. Healthcare providers are asked to report any suspected adverse reactions to:

- Acino Pharma (Pty) Ltd: E-mail: drugsafety_ZA@acino.swiss
  or
- SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms:

Side effects may be elicited or exacerbated in overdosage.

Management:

If overdosage occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 21.12 Hormone inhibitor.

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues; Somatostatin and analogues.

ATC code: H01CB03.

5.1 Pharmacodynamic properties

Lanreotide is an octapeptide analogue of natural somatostatin.

Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions.

It shows high binding affinity for human somatostatin receptors (SSTR) 2 and 5, and reduced affinity for human SSTR 1, 3 and 4. Activity at SSTR 2 and 5 is the primary mechanism considered to be responsible for growth hormone (GH) inhibition.

Lanreotide 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-hydroxyindoleacetic acid) in patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs) and with elevated levels of these tumour markers.

Lanreotide inhibits meal-induced increases in superior mesenteric arterial blood flow and portal venous blood flow.

Lanreotide reduces prostaglandin E1-stimulated jejunal hydroelectrolytic secretion.

Lanreotide reduces prolactin levels in patients treated long term.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lanreotide after intravenous administration in healthy volunteers are consistent with a short duration of action: steady-state volume of distribution of 13 L, clearance of 20 L/h, terminal half-life of 2,5 hours and mean residence time was 0,68 hours.

Lanreotide administered in the form of lanreotide Autogel by the subcutaneous route in healthy volunteers at doses of 60 mg, 90 mg and 120 mg showed a terminal elimination half-life and mean residence time of approximately 4 weeks.

Plasma concentrations plotted against the dose administered are almost log-linear with slight individual variations. Absolute bioavailability is approximately 60 %.

After a single subcutaneous injection of lanreotide Autogel 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 %.
Lanreotide Autogel releases active substance over 28 days.

In a population PK analysis of the GEP-NET study, 290 patients receiving lanreotide Autogel 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 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 impairment:
Subjects with severe renal impairment showed an approximately 2-fold decrease in total clearance of lanreotide Autogel, with a consequent increase in half-life and AUC.
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 lanreotide Autogel.
GEP-NET patients with severely impaired renal function were not studied.

Hepatic impairment:
Subjects with hepatic impairment have shown an increase in volume of distribution and mean residence time. In subjects with moderate to severe hepatic impairment, a reduction in clearance was observed (30 %).

No GEP-NET patients with hepatic impairment (as per Child-Pugh score) were studied.

Elderly patients:

Elderly subjects showed an increase in half-life and mean residence time compared with healthy young subjects. Due to the wide therapeutic window of lanreotide Autogel, it is not necessary to adapt the dose in these circumstances.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid (for pH adjustment),

Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Store at 2 °C – 8 °C (refrigerator) in its 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.

After opening the protective laminated bag, SOMATULINE AUTOGEL should be administered immediately.

6.4 Special precautions for storage

Do not freeze.

Do not remove from the carton until required for use.

Keep out of reach of children.

6.5 Nature and contents of container

A carton containing one 0,5 mL polypropylene pre-filled syringe fitted with an automatic safety system with a plunger stopper made from grey bromobutyl rubber, coated with silicone, and a stainless steel needle 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.

A box of one 0,5 mL pre-filled syringe with an attached needle (1,2 mm x 20 mm).

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106, 16th Road

Midrand

1686

8. REGISTRATION NUMBERS

SOMATULINE AUTOGEL 60: 45/21.12/1022

SOMATULINE AUTOGEL 90: 45/21.12/1023

SOMATULINE AUTOGEL 120: 45/21.12/1024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 31 July 2014

10. DATE OF REVISION OF THE TEXT

16 January 2025