Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Myrelez 90 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lanreotide (I.N.N.), 90 mg (as acetate)
Each prefilled syringe contains a supersaturated solution of lanreotide acetate corresponding to 0.246 mg lanreotide base/mg of solution, which ensures an actual injection dose of 90 mg of lanreotide.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in a prefilled syringe.
White to pale yellow semi-solid formulation practically free of foreign particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Myrelez is indicated for:
• The 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 otherwise require medical treatment.
• 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 (see section 5.1).
• The treatment of symptoms associated with neuroendocrine (particularly carcinoid) tumours.

4.2 Posology and method of administration

Posology

Acromegaly
The recommended starting dose is 60 mg to 120 mg administered every 28 days.
The dose may be varied according to the patient's response (judged by symptomatology and / or biochemical effect) or by the patient's possible experience with somatostatin analogues.
For example, in patients previously treated with lanreotide 30 mg with a dose every 14 days, the initial dose of Myrelez should be 60 mg every 28 days, and in patients previously treated with lanreotide 30 mg with a dose every 10 days, the initial dose of Myrelez should be 90 mg every 28 days.
The dose should be individualised according to the response of the patient (as judged by a reduction in symptoms and/or a reduction in GH and/or IGF-1 levels).
For patients in whom clinical symptoms and biochemical parameters are not adequately controlled, the dose of Myrelez may be increased to a maximum of 120 mg at 28-day intervals.
If complete control is obtained (based on GH levels under 1 ng/ml, normalised IGF1 levels and/or disappearance of symptoms), the dose may be decreased.
Patients well controlled on a somatostatin analogue can alternatively be treated with Myrelez 120 mg every 42-56 days (6 to 8 weeks).
Long term monitoring of symptoms, GH and IGF-1 levels should be routinely carried out in all patients.

Treatment of grade 1 and a subset of grade 2 (Ki67 index up to 10%) gastroenteropancreatic neuroendocrine tumours of midgut, pancreatic or unknown origin where hindgut sites of origin have been excluded, in adult patients with unresectable locally advanced or metastatic disease
The recommended dose is one injection of Myrelez 120 mg administered every 28 days. The treatment with Myrelez should be continued for as long as needed for tumour control.

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

Renal and /or hepatic impairment

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

Elderly patients

In elderly patients, no dosage adjustment is necessary due to the wide therapeutic window of lanreotide (see section 5.2).

Paediatric population

Myrelez is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Method of administration

Myrelez is administered by deep subcutaneous injection in the superior external quadrant of the buttock or in the upper outer thigh.
For patients who receive a stable dose of Myrelez**,** and after appropriate training, the product may be administered either by the patient or by a trained person. In case of self-injection, the injection should be given in the upper outer thigh.
The decision regarding administration by the patient or a trained person should be taken by a healthcare professional.
Regardless of the injection site, the skin should not be folded and the needle should be inserted rapidly and to its full length, perpendicularly to the skin.
The injection site should alternate between the right and left side.

4.3 Contraindications

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

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. 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 show that lanreotide, like somatostatin and other somatostatin analogues, inhibits the 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 and any anti-diabetic treatment should be adjusted accordingly.
Slight decreases in thyroid function have been seen during treatment with lanreotide in patients with acromegaly, although clinical hypothyroidism is rare (<1%). Tests of thyroid function should be done where clinically indicated.
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 cardiac disorders prior to lanreotide treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with lanreotide in patients with bradycardia (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interactions

The pharmacological gastrointestinal effects of lanreotide may result in the reduction of the intestinal absorption of co-administered drugs including ciclosporin. Concomitant administration of ciclosporin with lanreotide may decrease the relative bioavailability of ciclosporin and therefore may necessitate the adjustment of ciclosporin dose to maintain therapeutic levels.
Interactions with highly plasma bound drugs are unlikely in view of the moderate binding of lanreotide to serum proteins.
Limited published data indicate that concomitant administration of somatostatin analogues and bromocriptine may increase the availability of bromocriptine.

Concomitant administration of bradycardia inducing drugs (e.g. beta blockers) may have an additive effect on the slight reduction of heart rate associated with lanreotide. Dose adjustments of such concomitant medicines 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 metabolised by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals showed no evidence of teratogenic effects associated with lanreotide during organogenesis.
Data on a limited number of pregnant women exposed to lanreotide indicate no adverse effects of lanreotide on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available.
Because animal studies are not always predictive of human responses, lanreotide should be administered to pregnant women only if clearly needed.

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

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

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

4.8 Undesirable effects

Undesirable effects reported by patients suffering from acromegaly and GEP-NETs treated with lanreotide in clinical trials are listed under the corresponding body organ systems according to the following classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100).
The most commonly expected adverse drug reactions following treatment with lanreotide are gastrointestinal disorders (most commonly reported are diarrhoea and abdominal pain, usually mild or moderate and transient), cholelithiasis (often asymptomatic) and injection site reactions (pain, nodules and indurations).
The profile of undesirable effects is similar for all indications.

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Post-marketing safety experience (frequency not known)**
Infections and infestations				Injection site abscess
Metabolism and nutrition disorders		Hypoglycaemia, decreased appetite**, hyperglycaemia, diabetes mellitus		
Psychiatric disorders			Insomnia*	
Nervous system disorders		Dizziness, headache, lethargy**		
Cardiac disorders		Sinus bradycardia*		

Vascular disorders			Hot flushes*	
Gastrointestinal disorders	Diarrhoea, loose stools*, abdominal pain	Nausea, vomiting, constipation, flatulence, abdominal distension, abdominal discomfort, dyspepsia, steatorrhoea**	Faeces discoloured*	Pancreatitis
Hepatobiliary disorders	Cholelithiasis	Biliary dilatation*		Cholecystitis, cholangitis
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 reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

If overdose occurs, symptomatic management is indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

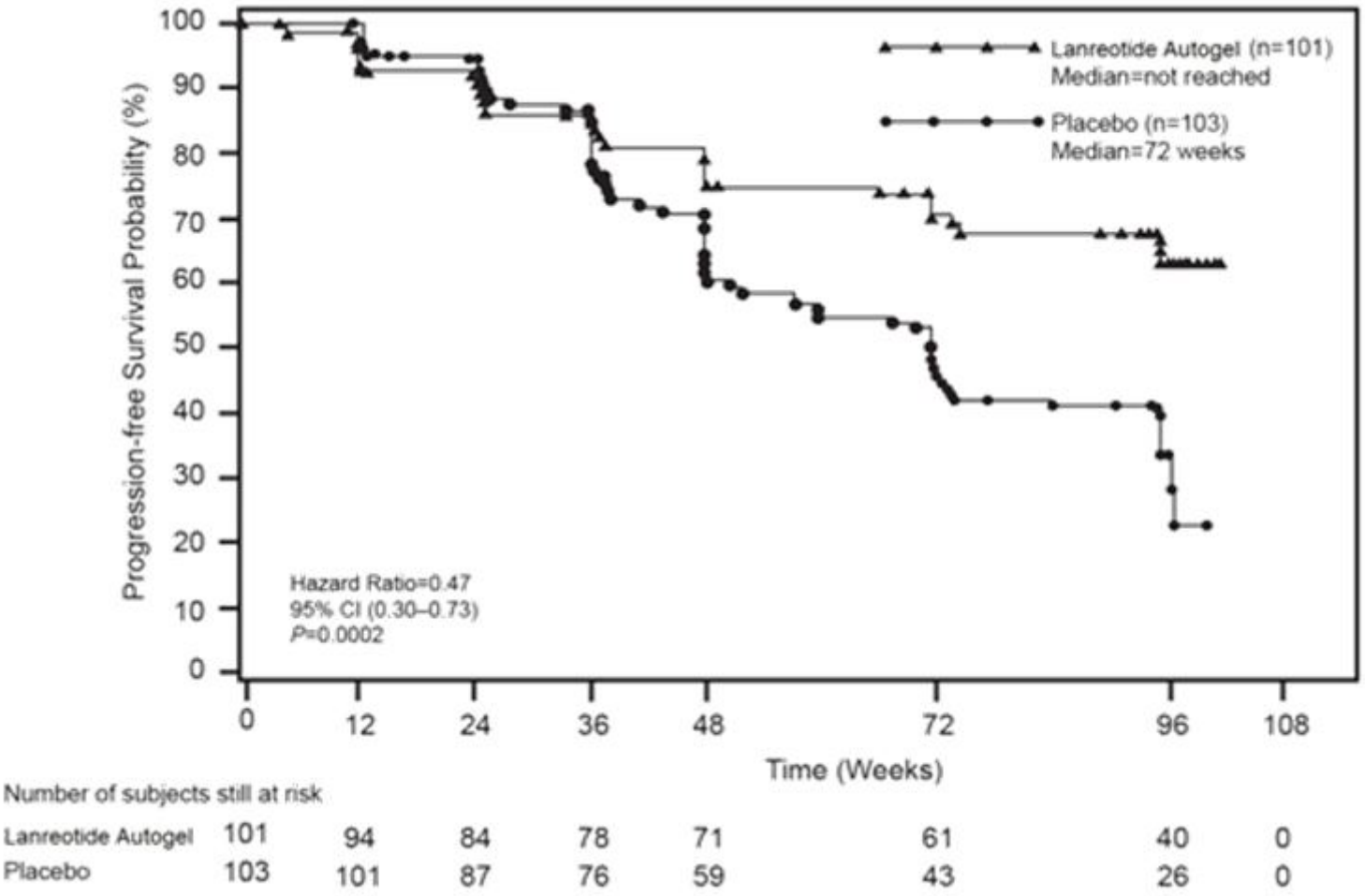
Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatostatin and analogues, ATC code: H01C B03

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 SSTR 1, 3 and 4. Activity at human SSTR 2 and 5 is the primary mechanism considered to be responsible for GH inhibition. Lanreotide is more active than natural somatostatin and shows a longer duration of action.
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 markedly inhibits meal-induced increases in superior mesenteric artery blood flow and portal venous blood flow. Lanreotide significantly reduces prostaglandin E1-stimulated jejunal secretion of water, sodium, potassium and chloride. Lanreotide reduces prolactin levels in patients with acromegaly patients treated long term.
In an open-label study, lanreotide 120mg was administered every 28 days for 48 weeks in 90 previously untreated acromegalic patients diagnosed with pituitary macroadenoma. Patients expected to require pituitary surgery or radiotherapy during the study period were excluded.
A reduction in tumour volume of ≥ 20% was observed in 63% of the patients (95% CI: 52%-73%). At week 48, 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. Most patients reported a clear relief of acromegaly symptoms such as fatigue, excess perspiration, arthralgia and soft tissue swelling. Both early and sustained reduction of tumour volume as well as GH and IGF-1 levels were observed from week 12 onwards.
A phase III, 96-week, fixed duration, randomized, double-blind, multi-centre, placebo-controlled trial of lanreotide was conducted in patients with gastroenteropancreatic neuroendocrine tumours to assess the antiproliferative effect of lanreotide. Patients were randomized 1:1 to receive either lanreotide 120 mg 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 a hepatic tumour load ≤10%, 14.5% had a hepatic tumour load > 10 and ≤25% and 33% had a 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
lanreotide (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

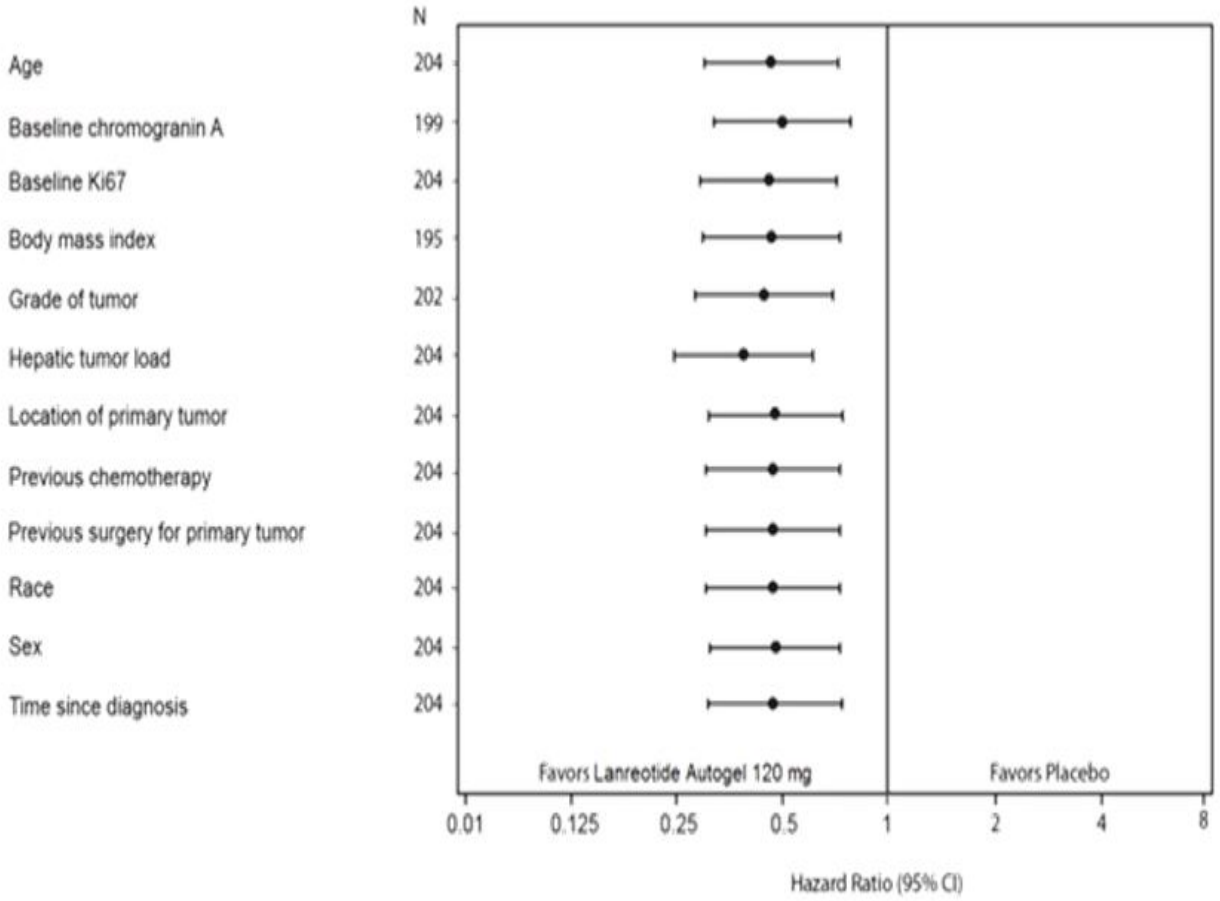
Figure 1: Kaplan-Meier Progression Free Survival Curves



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 lanreotide 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 lanreotide, in the extension study, occurred in 45.6% (47/103) of the patients**.**

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing lanreotide in all subsets of the paediatric population in acromegaly and pituitary gigantism (see section 4.2 for information on paediatric use). The European Medicines Agency has listed gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, phaechromocytoma) on the list of class waivers.

5.2 Pharmacokinetic properties

Intrinsic pharmacokinetic parameters of lanreotide after intravenous administration in healthy volunteers indicated limited extravascular distribution, with a steady-state volume of distribution of 16.1L. Total clearance was 23.7L/h, terminal half-life was 1.14 hours and mean residence time was 0.68 hours.
In studies evaluating excretion, less than 5% of lanreotide was excreted in urine and less than 0.5% was recovered unchanged in faeces indicating some biliary excretion.
After deep subcutaneous administration of lanreotide 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, respectively. These values of Cmax 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 first-order kinetics with a terminal elimination half-life of 23.3, 27.4 and 30.1 days respectively. 4 weeks after the administration mean lanreotide serum levels were 0.9, 1.11 and 1.69ng/mL respectively. Absolute bioavailability was 73.4, 69.0 and 78.4%, respectively.
After deep subcutaneous administration of lanreotide 60, 90 and 120 mg to patients with acromegaly, lanreotide concentrations increase to achieve average maximum serum concentrations of 1.6, 3.5 and 3.1ng/mL, respectively. These values of Cmax 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 Cmax at steady state were 3.8, 5.7 and 7.7ng/mL for 60, 90 and 120 mg respectively, the average Cmin values obtained being 1.8, 2.5 and 3.8ng/mL. The peak trough fluctuation index was moderate ranging from 81 to 108%.
Linear pharmacokinetic release profiles were observed after deep subcutaneous administration of lanreotide 60, 90 and 120 mg in patients with acromegaly.
Trough lanreotide serum levels obtained after three deep subcutaneous injections of lanreotide 60, 90 or 120 mg given every 28 days are similar to the steady-state trough lanreotide serum levels obtained in patients with acromegaly previously treated with intramuscular administrations of lanreotide 30 mg prolonged release microparticles every 14, 10 or 7 days, respectively.
In a population PK analysis in 290 GEP-NET patients receiving lanreotide 120 mg, rapid initial release was seen with mean Cmax 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 lanreotide 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 Cmax 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.
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. 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.
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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections.
Glacial acetic acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After opening the protective aluminum pouch, the product should be administered immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C) in the original package in order to protect from light.

The product can, provided it has been stored in the sealed pouch at a maximum temperature of 40 ° C for up to a total of 24 hours, be returned to the refrigerator (the number of temperature fluctuations must not exceed three) for continued storage and later use.

6.5 Nature and contents of container

Myrelez is supplied in a pre-filled syringe (polypropylene with thermoplastic elastomer rubber plunger stopper sealed with polypropylene cap) placed in a plastic tray and sealed inside an aluminum pouch and a separately packed automatic single use needle-safe device. Both are packaged inside a cardboard box.
Box of one 0.5 mL syringe with one co-packaged safety needle (1.2 mm x 20 mm).
Multipack with 3 boxes, each containing one 0.5 mL syringe with one co-packaged safety needle (1.2 mm x 20 mm).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution for injection in a pre-filled syringe is ready for use.
For immediate and single use following first opening. Do not use if the pouch is damaged or opened.
It is important that the injection of the product is performed exactly according to the instructions in the package leaflet.
The used injection device should be disposed of in a designated sharps container.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/039/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd July 2021

10 DATE OF REVISION OF THE TEXT