PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ADVANZ Pharma Group's Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe (Lanreotide)

This is a summary of the risk management plan (RMP) for ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe. The RMP details important risks of ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe, how these risks can be minimised, and how more information will be obtained about lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe risks and uncertainties (missing information).

ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe should be used.

I. The medicine and what it is used for

Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe is authorised 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 goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalize these values.
- 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).
- symptoms associated with neuroendocrine (particularly carcinoid) tumours.

It contains Lanreotide as the active substance and is administered by deep subcutaneous injection in the superior external quadrant of the buttock or in the upper outer thigh.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe, together with measures to minimise such risks and the proposed studies for learning more about lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ADVANZ Pharma Group's Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe (Lanreotide)

This is a summary of the risk management plan (RMP) for ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe. The RMP details important risks of ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe, how these risks can be minimised, and how more information will be obtained about lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe risks and uncertainties (missing information).

ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe should be used.

I. The medicine and what it is used for

Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe is authorised 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 goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalize these values.
- 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).
- symptoms associated with neuroendocrine (particularly carcinoid) tumours.

It contains Lanreotide as the active substance and is administered by deep subcutaneous injection in the superior external quadrant of the buttock or in the upper outer thigh.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe, together with measures to minimise such risks and the proposed studies for learning more about lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of lanreotide are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lanreotide. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Gastrointestinal effects • Gallstones (cholelithiasis) • Effects on glycoregulation • Effects on thyroid function • Slow heart rate (bradycardia) • Reactions at the injection site (administration site reactions) • Device use errors • Inflammation of the pancreas (pancreatitis) • Allergic reactions
Important potential risks	• Effects on bioavailability of concomitant medication • Liver disease (hepatic dysfunction) • Abnormal kidney function (renal impairment)
Missing information	• Pregnancy and breast-feeding (lactation) • Paediatric populations

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ADVANZ Pharma Group's Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe (Lanreotide)

This is a summary of the risk management plan (RMP) for ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe. The RMP details important risks of ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe, how these risks can be minimised, and how more information will be obtained about lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe risks and uncertainties (missing information).

ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ADVANZ Pharma Group's lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe should be used.

I. The medicine and what it is used for

Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe is authorised 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 goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalize these values.
- 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).
- symptoms associated with neuroendocrine (particularly carcinoid) tumours.

It contains Lanreotide as the active substance and is administered by deep subcutaneous injection in the superior external quadrant of the buttock or in the upper outer thigh.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe, together with measures to minimise such risks and the proposed studies for learning more about lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of lanreotide are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lanreotide. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Gastrointestinal effects • Gallstones (cholelithiasis) • Effects on glycoregulation • Effects on thyroid function • Slow heart rate (bradycardia) • Reactions at the injection site (administration site reactions) • Device use errors • Inflammation of the pancreas (pancreatitis) • Allergic reactions
Important potential risks	• Effects on bioavailability of concomitant medication • Liver disease (hepatic dysfunction) • Abnormal kidney function (renal impairment)
Missing information	• Pregnancy and breast-feeding (lactation) • Paediatric populations

II.B Summary of important risks

Important Identified Risks

Gastrointestinal effects	
Evidence for linking the risk to the medicine	Lanreotide works by lowering the levels of growth hormone and insulin-like growth factor-1. Lanreotide also blocks the release of some gastrointestinal hormones and intestinal secretions. [30] Somatostatin receptors are widely distributed, especially in the GI tract, and therefore side effects are not uncommon. Up to 50% of patients develop some initial GI complaints such as bloating and loose stools, but typically these wanes with time.[31]
Risk factors and risk groups	• Age • History of ulcers • Smoking • Alcohol use
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.8 • PL Section: 4 **Additional risk minimisation measures** • None proposed

Cholelithiasis	
Evidence for linking the risk to the medicine	Lanreotide, like somatostatin, decreases cholecystokinin secretion, gall bladder contractility and bile secretion, perhaps accounting for the high rate of gall bladder sludge and stone formation with long term use. In long term studies, cholelithiasis developed in 20% to 33% of lanreotide treated patients. In some instances, symptomatic cholecystitis occurred which can be accompanied by mild-to-moderate elevations in serum enzymes and bilirubin. However, most lanreotide associated gallstones were asymptomatic.[32]

Risk factors and risk groups	• Obesity • Family History • Rapid weight loss • Excess cholesterol and bilirubin in bile • Abnormal gallbladder functioning
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.4, 4.8 • PL Section: 2, 4 **Recommendation in Section 4.4 of SmPC**: • Lanreotide may reduce gallbladder motility and lead to gallstone formation. Therefore, patients may need to be monitored periodically. **Additional risk minimisation measures** • None proposed

Effects on glycoregulation	
Evidence for linking the risk to the medicine	GH excess affects insulin sensitivity and gluconeogenesis and can alter pancreatic β-cell function, leading to a derangement of glucose metabolism in a considerable percentage of acromegaly patients. Indeed, impaired glucose tolerance (IGT) or diabetes mellitus (DM) are considered a frequent and—in many cases—an early manifestation of acromegaly. On the other hand, drugs used to treat acromegaly may cause glucose tolerance abnormalities, regardless of disease control. In a recent meta-analysis of 47 prospective interventional studies including 1,297 acromegaly patients, first-generation SSAs were found to affect glycaemic status by reducing insulin, increasing glucose levels after OGTT and HbA1c, with a significant increase of FPG only when they were used as second-line treatment. [33]
Risk factors and risk groups	• Family history of diabetes • Higher BMI • Older Age
Risk minimisation measures	**Routine risk minimisation measures:**

	• SPC Section: 4.4, 4.8 • PL Section: 2, 4 **Additional risk minimisation measures** • None proposed

Effects on thyroid function	
Evidence for linking the risk to the medicine	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. Lanreotide inhibits the nocturnal increase in thyroid-stimulating hormone (TSH) seen in healthy subjects. [34]
Risk factors and risk groups	• Age • Sex • Family history of thyroid disease
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.4 • PL Section: 2 **Recommendation in S 4.4 of SmPC**: • Thyroid function tests are recommended where clinically indicated. **Additional risk minimisation measures** • None proposed

Bradycardia	
Evidence for linking the risk to the medicine	Patients with heart disorders prior to treatment may more easily develop sinus bradycardia, where the heart beats fewer than 60 times per minute. Patients with acromegaly have a higher risk of bradycardia. In a group of 81 patients affected by GEP-NENs treated with LAN Autogel, the incidence of heart rate <60 bpm was 23% (vs 16% in placebo group), while the incidence of episodes of

	heart rate <50 bpm as well as adverse event of bradycardia was 1% in each group. This finding can be explained by the activity of the bulbospinal neurons in the rostral ventrolateral medulla (RVLM), which are known to be critical for the maintenance of sympathetic vasomotor tone and normal cardiovascular reflex function. In particular, RVLM presympathetic neurons that express SSTR 2A are essential for maintaining and potentially generating sympathetic vasomotor tone. In rats, microinjection of either SST or LAN into the RVLM causes a dose-dependent sympathoinhibition, hypotension, and bradycardia that is blocked by the SSTR 2 antagonist. [35]
Risk factors and risk groups	• Underlying heart disease • Hypothyroidism • Heart tissue damage related to aging • Damage to heart tissues from heart disease or heart attack.
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.4, 4.5, 4.8 • PL Section: 2 **Recommendation in Section 4.4 of SmPC**: • Care should be taken when initiating treatment with lanreotide in patients with bradycardia. **Additional risk minimisation measures** • None proposed

Administration site reactions	
Evidence for linking the risk to the medicine	Patients may experience injection site reactions, which are among the most common side-effects of lanreotide treatment. The reactions may include pain, itching, hardening of the skin, and the formation of nodules (small collections of tissue that can be felt). These reactions are seldom severe.
Risk factors and risk groups	• Not available

Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.2, 4.8 • PL Section: 2, 4 **Recommendation in Section 4.2 of SmPC**: • Regardless of the 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. **Additional risk minimisation measures** • None proposed

Device Use Errors	
Evidence for linking the risk to the medicine	A study[38] was conducted during August 2018 to validate the user interface of a pre-filled safety syringe (PFSS) from a Human Factors (HF) perspective. A total of 45 subjects participated in this study. Out of 45 participants, 14 were observed to perform a use error at the stage in the administration process. Participants were observed to perform use errors during the simulated use scenario. There were four different use errors observed which include that participants did not insert the needle, then it gradually inserted whilst the plunger was being pushed, participants inserted the needle part-way or did not insert the needle at all or they inserted the needle and then removed immediately without administering the dose. The outcome of the study showed that there were use errors amongst the different user groups and for a variety of tasks.
Risk factors and risk groups	Not available
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section: 2 • PL Section: 3 **Additional risk minimisation measures**

	• None proposed

Pancreatitis	
Evidence for linking the risk to the medicine	Pancreatic non-functional tumours are some of the more common NETs, comprising 20% of tumours in one survey of 837 patients with NETs. Patients with non-functional pancreatic tumours may experience pancreatitis. However, information on the prevalence of pancreatitis in these patients is limited to individual case reports, indicating that it is a rare occurrence.
Risk factors and risk groups	• Smoking • Gallstones • Cancer of the pancreas • Cystic fibrosis • Alcohol abuse
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.8 • PL Section: 4 **Additional risk minimisation measures** • None proposed

Allergic reactions	
Evidence for linking the risk to the medicine	Lanreotide commonly causes skin reactions at the site of injection, although life-threatening reactions were not reported in the clinical trials. Patients who experience an allergic reaction after treatment with lanreotide should stop treatment and avoid further use of the drug.
Risk factors and risk groups	• Age • Gender • Genetics

Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.3, 4.8 • PL Section: 2, 4 **Additional risk minimisation measures** • None proposed

IMPORTANT POTENTIAL RISKS

Effects on bioavailability of concomitant medication	
Evidence for linking the risk to the medicine	The gastrointestinal effects of Somatuline Autogel may reduce the intestinal absorption of co- administered drugs. Limited published data indicate that somatostatin analogues might decrease the metabolic clearance of compounds known to be metabolized 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 medicinal products mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. terfenadine) should therefore be used with caution. [36]
Risk factors and risk groups	• Peritoneal carcinomatosis • Liver Tumors
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.5 • PL Section: 2 **Additional risk minimisation measures** • None proposed

Hepatic dysfunction	
Evidence for linking the risk to the medicine	In hepatic impairment, an increase in Volume of Distribution, Mean Residence Time, AUC, and half-life were observed. Clearance was reduced by 30% in

	moderate to severe hepatically impaired patients with moderate to severe hepatic impairment should begin treatment with lanreotide 60 mg. Caution should be exercised when using this agent in patients with moderate or severe hepatic impairment for an extended dosing interval.[37]
Risk factors and risk groups	• Diabetes • Peritoneal carcinomatosis • NET and pituitary thyrotropic adenoma
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.8 • PL Section: 2, 4 **Additional risk minimisation measures** • None proposed

Renal Impairment	
Evidence for linking the risk to the medicine	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. It is recommended that patients with moderate or severe renal impairment receive a starting dose of lanreotide of 60 mg.
Risk factors and risk groups	• Age> 60 years • Diabetes • Pre-existing renal impairment • Dehydrated • Exposed to other kidney toxins • Heart failure • Sepsis
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.2 **Additional risk minimisation measures** • None proposed

MISSING INFORMATION

Pregnancy and lactation	
Evidence for linking the risk to the medicine	As per Section 4.6 of the SPC, Lanreotide has not been studied in pregnant or breastfeeding women. Lanreotide should not be used during pregnancy, unless it is clearly needed. Caution must be taken if lanreotide is used during breast-feeding.
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.6 • PL Section: 2 **Additional risk minimisation measures** • None proposed

Paediatric populations	
Evidence for linking the risk to the medicine	As per Section 4.2 of the SPC, Lanreotide is not recommended for use in children and adolescents due to lack of data on safety and efficacy.
Risk minimisation measures	**Routine risk minimisation measures:** • SPC Section: 4.2 • PL Section: 2 **Additional risk minimisation measures** • None proposed

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Lanreotide 60mg, 90mg, 120mg, solution for injection in a prefilled syringe'.