Medicines and Healthcare products Regulatory Agency

Safeguarding public health

Assessment Report
Mutual recognition Procedure

OVERVIEW

Ipstyl LA 60, 90 and 120mg Solution for Injection

Lanreotide Acetate

UK/H/0723/001-003

Applicant: Ipsen Ltd

Date: 14th December 2004

TABLE OF CONTENTS

COVER PAGE

Name of the product in the Reference Member State	Ipstyl LA 60, 90 and 120mg Solution for Injection
Name of the active substance	Lanreotide Acetate
Pharmacotherapeutic classification (ATC code)	H01C B03
Pharmaceutical form and strength	Solution for Injection, 60, 90 and 120mg
Reference numbers for the Mutual Recognition Procedure	
Reference Member State	United Kingdom
Member States concerned	Germany
Authorisation holder's name and address	Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK.
Names and addresses of manufacturers of dosage form	[redacted] Redacted according to Section 43, FOI Act [redacted] Redacted according to Section 43, FOI Act
Name and address of manufacturer responsible for batch release in the EEA	Ipsen Pharma Biotech (IPB), Parc d'Activités du Plateau de Signes, Chemin Départemental n°402, 83 870 SIGNES, France. Beaufour Ipsen Industrie (BII), 20 rue Ethe Virton, 28100 DREUX, France.
Date of first authorisation	26th May 2004
Marketing Authorisation numbers	PL 06958/0020-22
Date of Assessment Report	14th December 2004
Reference Member State Contact Point	[redacted] Redacted according to Section 40, FOI Act
Assessors:	
Quality (Module 3)	[redacted] Redacted according to Section 40, FOI Act
Non-Clinical (Module 4)	
Clinical (Module 5)	

EUDRATRACK DETAILS

60mg

Level 1	Abridged
Level 2	Initial application
Level 3	Full dossier, Article 8.3(i)
Level 4	Chemical substance
Level 5	Prescription only

90mg

Level 1	Abridged
Level 2	Initial application
Level 3	Full dossier, Article 8.3(i)
Level 4	Chemical substance
Level 5	Prescription only

120mg

Level 1	Abridged
Level 2	Initial application
Level 3	Full dossier, Article 8.3(i)
Level 4	Chemical substance
Level 5	Prescription only

I RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Ipstyl LA Solution for Injection in the treatment of 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, could be approved. A national marketing authorisation was granted on 26th May 2004.

II EXECUTIVE SUMMARY

II.1 Problem statement

Acromegaly

Acromegaly is a chronic debilitating disease that results when the pituitary gland produces excess growth hormone (GH), usually from a pituitary adenoma. It most commonly affects middle-aged adults and can result in serious illness and premature death. Once recognised, acromegaly is treatable in most patients, but because of its slow and insidious onset, it is frequently misdiagnosed.

Small pituitary adenomas are common. During autopsies, they are found in up to 25 percent of the U.S. population. However, these tumours rarely cause symptoms or produce excessive GH or other pituitary hormones. It is estimated that 3 out of every million people develop acromegaly each year and that 40 to 60 out of every million people suffer from the disease at any time. However, because the clinical diagnosis of acromegaly is often missed, these numbers probably underestimate the frequency of the disease.

Acromegaly is caused by prolonged overproduction of GH by the pituitary gland. GH is part of a cascade of hormones that regulate the physical growth of the body. This cascade begins in the hypothalamus, which produces hormones that regulate the pituitary. One of these, growth hormone-releasing hormone (GHRH), stimulates the pituitary gland to produce GH. Another hypothalamic hormone, somatostatin, inhibits GH production and release. Secretion of GH by the pituitary into the bloodstream causes the production of insulin-like growth factor 1 (IGF-1), in the liver. IGF-1 is the factor that actually causes the growth of bones and other tissues of the body. IGF-1, in turn, signals the pituitary to reduce GH production. GHRH, somatostatin, GH, and IGF-1 levels in the body are tightly regulated by each other and by sleep, exercise, stress, food intake and blood sugar levels. If the pituitary continues to make GH independent of the normal regulatory mechanisms, the level of IGF-1 continues to rise, leading to bone growth and organ enlargement. The excess GH also causes changes in sugar and lipid metabolism and can cause diabetes.

The classic signs and symptoms of acromegaly include skeletal overgrowth deformities, arthropathy and neuropathy. Up to 60% of patients suffer severe headaches, 50% have abnormal glucose tolerance, more than 50% have upper respiratory obstruction, 25% have cardiac disease and 30% hypertension. Acromegaly, as well as being associated with a reduced quality of life, is also associated with a two to three fold increase in mortality.

Treatment

The goals of acromegaly treatment are to reduce GH production to normal levels, to relieve the pressure that the growing pituitary tumour exerts on the surrounding brain areas, to

preserve normal pituitary function, and to reverse or ameliorate the symptoms of acromegaly. Currently, treatment options include surgical removal of the tumour, drug therapy, and radiation therapy of the pituitary.

II.2 About the product

Ipstyl LA is a long acting formulation of lanreotide. Lanreotide is an octapeptide, an analogue of the naturally occurring hormone, somatostatin. Lanreotide lowers the levels of Growth Hormone (GH) and Insulin-like Growth Factor-1 (IGF-1) and inhibits the release of some gastro-intestinal hormones and intestinal secretions.

Ipstyl LA solution for injection is indicated for the treatment of individuals with acromegaly when the circulating levels of GH and /or 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 normalise these treatments.

Ipstyl LA solution for injection is a white to off-white, translucent and viscous supersaturated solution in a pre-filled syringe, ready for use. The solution should be injected via the deep sub-cutaneous route in the superior external quadrant of the buttock. The skin should not be folded. The needle should be inserted rapidly to its full length, perpendicularly to the skin.
Ipstyl LA is supplied in a clear polypropylene pre-filled syringe and is available in three strengths, 60mg, 90mg and 120mg.

Ipstyl LA should only be administered by a nurse or doctor and is not recommended for use in children.

II.3 The development programme

This application is submitted by Ispen Limited via the Decentralised (Mutual Recognition) Procedure, based upon Mutual Recognition of United Kingdom Product Licences (UK MA PL 06958/0020-22) held by the applicant, which were approved on 26th May 2004. The applicant now seeks Marketing Authorisation in Germany where the proposed product name is Somatuline Autogel 69/90/120 mg. The original application was submitted to the UK Licensing Authority as Ipstyl LA 60/90/120 mg, Solution for Injection.

These applications relate to products identical to ones currently approved in the UK - Somatuline Autogel 60mg, 90mg & 120mg (PL 06958/0013-0015). The applications for the latter were abridged line extensions of another UK approved product, Somatuline LA (PL 06958/0018). These present UK applications for Ipstyl LA are being submitted solely to support the mutual recognition in Germany. Ipsen Limited does not plan to market product against these licenses in the UK, it will continue to market Somatuline Autogel as currently approved. The Somatuline LA product on which the original UK line extension application for Somatuline Autogel was based is not approved in Germany. Therefore, the Company has prepared this stand-alone dossier combining the data from Somatuline LA and Somatuline Autogel.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No toxicity was demonstrated, and no new toxicological problems for these products were found.

The results of the nonclinical studies of lanreotide support the conclusion that lanreotide Autogel possesses therapeutic potential in the management of acromegaly and that is can be safely administered to humans.

Clinical studies on Ipstyl LA 60, 90 and 120mg Solution for Injection were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Ipstyl LA 60, 90 and 120mg Solution for Injection provides satisfactory clinical benefits.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

[redacted] Satisfactory GMP inspections have been performed on this site as confirmed by the covering letter from Irish Medicines Board of 15-Oct-2003 regarding the IMB inspection on 7th October 2003. This certificate remains valid until the 6th October 2006.

Redacted according to Section 43, FOI Act

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The drug substance is a synthetic octapeptide, an analogue of natural somatostatin, containing a disulphide bond between the two cysteine residues and the D- forms of both β-Nal and Trp.

Lanreotide acetate is currently manufactured and released by [redacted] Acceptable standards of GMP are in place at this site and copies of the certification issued by the IMB have been received.

Redacted according to Section 43, FOI Act

Drug product

The medicinal product consists of a pre-filled syringe containing a supersaturated solution obtained by mixing lanreotide and water for injections, to a final concentration of 0.246mg/mg. A deep subcutaneous injection allows the prolonged release of 60mg, 90mg or 120mg of lanreotide over a period of at least 28 days. The composition of the product is very simple (containing only lanreotide and water for injections Ph Eur) and presents no issues.

The manufacture and control of the final product are considered suitable for the indications proposed. The overall quality of the final is satisfactory for its intended purpose.

III.2 Non-clinical aspects

Pharmacology

Overall, the pharmacodynamic studies demonstrated that lanreotide possesses a high and selective affinity for somatostatin receptors, a potent inhibitory effect on GH release, and an extended duration of action relative to somatostatin.

Pharmacokinetics

Assessment of the pharmacokinetic characteristics of lanreotide revealed that the drug is promptly and efficiently absorbed from s.c. or i.m. sites, it is extensively metabolised with metabolites being excreted in the faeces and urine and there is no evidence of bio-accumulation during chronic administration.

Toxicology

The results of nonclinical toxicology studies revealed that the drug possesses little, if any potential for producing organ-specific toxicity. Toxicological consequences or repeated high does in rats and dogs were related to growth inhibition and delayed maturation. There was no evidence of major effects of the drug on fertility or reproductive behaviour other than increased resorption at doses. leading to decreases in maternal body weight gain. Similarly, there was no evidence of teratogenic potential in rats or rabbits, even at maternally toxic doses that also caused embryotoxicity/lethality. There was no evidence of a mutagenic effect of the compound.

III.3 Clinical aspects

Pharmacokinetics

The pharmacokinetics of lanreotide has been determined in numerous healthy volunteer studies following single s.c., i.v. and continuous s.c. dosing of the immediate release formulation. A number of studies were performed reflecting a general pharmacokinetic profile of rapid absorption, a short mean residence time and limited extravascular distribution and rapid elimination.

Pharmacodynamics

Pharmacodynamic studies investigating both primary (inhibition of GH and IGF-1) and secondary effects of lanreotide IR and lanreotide Microparticle formulation (lanreotide PR 30mg) have been conducted in healthy volunteers and in acromegaly patients.

Primary pharmacology studies using lanreotide IR showed that lanreotide dose-dependently reduced spontaneous GH secretion in healthy volunteers and acromegalic patients, however only continuous administration of lanreotide IR produced a sustained reduction in GH levels in acromegalic patients. In healthy volunteers, the effect of a single dose of 30mg Microparticle formulation on GH was small (significant only on day 1 after injection). However, a single dose of lanreotide PR 30mg significantly reduced GH and IGF-1 levels in acromegalic patients up to 17 and 14 days after administration respectively.

Secondary pharmacological studies were also conducted, examining he effect of lanreotide on glycoregulation, secretion of digestive hormones, intestinal transit, renal and splanchnic blood

flow, and secretion of other hormones (e.g., cortisol). In all cases, the effects of lanreotide were consistent with those of somatostatin.

No pharmacodynamic studies were conducted specifically with the lanreotide Autogel formulation since the pharmacodynamic profile of lanreotide has been thoroughly investigated using immediate release and prolonged release Microparticle formulations.

Clinical efficacy

The applicant has satisfactorily demonstrated the efficacy of both lanreotide Microparticles and lanreotide Autogel in patients with acromegaly.

The main lanreotide Autogel efficacy study presented in this submission is [redacted], in which patients were switched from lanreotide Microparticles to lanreotide Autogel at fixed doses. These patients then went on to a second study ([redacted]) in which they received titrated doses of lanreotide Autogel for 12 months. This study demonstrated that lanreotide Autogel was no less effective than lanreotide Microparticles. Both treatments reduced levels of GH and IGF-1 in patients with acromegaly and were well tolerated.

Redacted according to Section 40, FOI Act

All of the studies conducted and included in this application were open label due to the small numbers of patients that were available for recruitment in this orphan indication. Each involved the treatment of a significant number of patients over a long duration, had validated databases and were conducted according to current Good Clinical Practice (GCP) guidelines.

Clinical safety

The focus of the safety analysis was on two pivotal Autogel studies. Study [redacted] investigated the switch from the widely marketed lanreotide Microparticle formulation of lanreotide to the lanreotide Autogel formulation. The second study, [redacted] was the follow on study from [redacted] and involved the recruitment of patients who had completed [redacted]. Data were also presented on supportive studies with lanreotide Autogel and lanreotide Microparticles.

Redacted according to Section 40, FOI Act

Lanreotide appeared to have good local tolerance in most patients with no adverse reactions being quoted as severe.

No deaths were reported during [redacted] and there were two deaths reported for study [redacted]. One during the study (infection of left hip prosthesis, abscess of hip joint) and one afterwards (enlarged nymph node left axial due to mammary carcinoma). Neither was considered related to the study medication.

Redacted according to Section 40, FOI Act

The applicant has satisfactorily demonstrated the safety of both lanreotide Microparticles and lanreotide Autogel in healthy subjects, patients with acromegaly and special populations.

IV SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Product Summary

1. TRADE NAME OF THE MEDICINAL PRODUCT

IPSTYL® LA 60 mg, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lanreotide (I.N.N.) 60 mg (as acetate).

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

White to off-white, translucent and viscous supersaturated solution in a pre-filled syringe, ready for use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IPSTYL® LA 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 goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalise these values.

4.2 Posology and method of administration

- <u>Posology</u>

In patients receiving a somatostatin analogue for the first time, the recommended starting dose is 60 mg of IPSTYL® LA administered every 28 days.

Thereafter, for all patients, 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 IGF1 levels).

If the desired response is not obtained, the dose may be increased.

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.

Long term monitoring of symptoms, GH and IGF1 levels should be undertaken as clinically indicated.

Hepatic/renal impairment and the elderly.
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 hepatic impairment, an increase in volume of distribution and mean residence time are observed, but there is no difference in total clearance or AUC. Elderly subjects show an increase in half-life and mean residence time compared with healthy young subjects. Due to the wide therapeutic window of lanreotide, it is not necessary to alter the dose in these circumstances.

Children.
Currently there is no experience of administration of IPSTYL® LA in children, therefore use of IPSTYL® LA in children cannot be recommended.

- **Method of administration**

IPSTYL® LA should be injected via the deep sub-cutaneous route in the superior external quadrant of the buttock. The skin should not be folded. The needle should be inserted rapidly to its full length, perpendicularly to the skin.

4.3 Contraindications

Hypersensitivity to lanreotide or related peptides.

4.4 Special warning and precautions for use

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and its analogues, inhibits the secretion of insulin and glucagon. Hence, patients treated with IPSTYL® LA may experience hypoglycaemia or hyperglycaemia. Blood glucose levels should be monitored when lanreotide treatment is initiated and treatment of diabetic patients should be accordingly adjusted. In insulin-dependent patients, insulin requirements may be reduced.

Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, although clinical hypothyroidism is rare (<1%). Tests of thyroid function should be done where clinically indicated.

Lanreotide may reduce gall bladder motility and gall bladder ultrasonography is therefore advised at the start of treatment and periodically thereafter. If gallstones do occur, they are generally asymptomatic. Symptomatic stones should be treated as medically indicated.

Lanreotide may lead to a decrease of heart rate without necessarily reaching the threshold of bradycardia (< 60 beats per minute) in patients without an underlying cardiac problem. In patients suffering from cardiac disorders prior to lanreotide initiation, sinus bradycardia may occur and therefore heart rate should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

The gastrointestinal effects of IPSTYL® LA may reduce the intestinal absorption of co-administered drugs.

Concomitant administration of lanreotide injection with cyclosporin may decrease blood levels of cyclosporin, hence blood levels of cyclosporin should be monitored.

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

4.6 Pregnancy and lactation

Reproductive studies in rats and rabbits at doses up to 33 times the human dose have failed to demonstrate a risk to the foetus; however there are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used in pregnant or breast-feeding women only if clearly needed.

Eleven pregnancies have been reported in patients who were being treated with lanreotide. Ten cases originated from patients with acromegaly and 1 case from a patient with neuroendocrine tumours. In five cases (four patients with acromegaly and one patient with neuroendocrine tumours) the course and outcome of the pregnancy were normal. In one case the outcome was a premature delivery, however, this patient suffered from arterial hypertension and she underwent pituitary surgery during pregnancy. In one case the patient decided to abort. The four remaining cases resulted in a miscarriage, however two of these cases were poorly documented and in no case could a causal relationship to lanreotide treatment be established.

4.7 Effects on ability to drive and use machines

No effects of IPSTYL® LA on ability to drive and use machines have been described.

4.8 Undesirable effects

The adverse reactions related to IPSTYL® LA during clinical trials are consistent with those seen with other prolonged release formulations of lanreotide, and are predominantly gastrointestinal. The most commonly reported adverse reactions in clinical trials are diarrhoea, abdominal pain, nausea, vomiting, dyspepsia, flatulence, cholelithiasis and headache. These reactions are usually mild and transient.

Undesirable effects are listed under the corresponding body organ systems according to the following classification: Very common >10%; common >1.0% to < 10%; uncommon > 0.1% to < 1.0%.

Metabolism and nutrition disorders
Common: Hypoglycaemia or hyperglycaemia, anorexia
Uncommon: Diabetes mellitus aggravated

Nervous system disorders
Very common: Headache
Common: Dizziness

Cardiac disorders
Common: Sinus bradycardia

Gastrointestinal disorders

Very common: Diarrhoea or loose stools, abdominal pain, nausea, vomiting, dyspepsia, flatulence
Common: Constipation
Uncommon: Acute pancreatitis, steatorrhoea, tenesmus

Hepato-biliary disorders
Very common: Cholelithiasis
Common: Bilirubin increased

Skin disorders
Uncommon: Allergic skin reaction, hair loss

General disorders and administration site conditions
Common: Fatigue, Injection site reaction
Uncommon: Injection site nodule, hot flushes, somnolence, leg pain, decreased libido, increased sweating

Reactions at the injection site may occur after the deep subcutaneous injection of IPSTYL® LA in the buttock. When specific enquiry was made, pain, redness, itching and induration were reported at the injection site 30 minutes after dosing in up to 8%, 5%, 5% and 19% of patients respectively. After 3 dosing intervals, these symptoms or signs were reduced to 6%, 2% 3% and 9% of patients or fewer. In all cases, the symptoms were described as mild.

Post-marketing safety experience has not identified other relevant information. Rarely post-injection episodes of malaise with signs of dysautonomia were reported. Rare cases of persisting induration at injection site were reported.

Cardiovascular effects including a myocardial infarction (see section 4.9 Overdose), high blood pressure episodes and ventricular tachycardia have also been reported in exceptional cases with other prolonged release formulations of lanreotide.

4.9 Overdose

In clinical trials, lanreotide has been administered in doses up to 15 mg per day without serious adverse events related to the treatment. Human experience of overdose of prolonged release forms of lanreotide is limited to one unconfirmed case report of overdose where a patient was reported to have taken one intramuscular injection of the 30 mg prolonged release formulation daily for two months (instead of 1 injection every 7 to 14 days). One week after stopping therapy the 52 year-old man with a history of acromegaly, diabetes mellitus and arterial hypertension suffered a fatal cardiac infarction.

If overdosage occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigrowth hormones, ATC code: H01C B03.

Lanreotide is an octapeptide analogue of natural somatostatin. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions. It shows high binding affinity for human somatostatin receptors (SSTR) 2, 3 and 5, and reduced affinity for human SSTR 1 and 4. Activity at SSTR 2 and 5 is the primary mechanism considered to be responsible for GH inhibition.

Lanreotide, like somatostatin, exhibits a general exocrine anti-secretory action. It inhibits the basal secretion of motilin, gastric inhibitory peptide and pancreatic polypeptide, but has no significant effect on fasting secretin or gastrin secretion. Lanreotide markedly inhibits meal-induced increases in superior mesenteric artery blood flow and portal venous blood flow. Lanreotide significantly reduces prostaglandin E1-stimulated jejunal secretion of water, sodium, potassium and chloride. Lanreotide reduces prolactin levels in acromegalic patients treated long term.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lanreotide after intravenous administration in healthy volunteers indicated limited extravascular distribution, with a steady-state volume of distribution of 13 l. Total clearance was 20 l/h, terminal half-life was 2.5 hours and mean residence time was 0.68 hours.

After a single subcutaneous injection of IPSTYL® LA 60 mg in healthy volunteers, a maximum serum concentration (Cmax) 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%.

After a single intramuscular injection of IPSTYL® LA 60 mg in healthy volunteers, a maximum serum concentration (Cmax) of 6.8 ± 3 ng/ml was reached after 15 hours, followed by a slow decrease (mean residence time: 23 ± 11 days, apparent half-life: 23 ± 9 days). The absolute bioavailability was 79 ± 10%.

Therefore the route of administration (subcutaneous or intramuscular) does not show any marked influence on the lanreotide pharmacokinetic profile.

After a single intramuscular injection of IPSTYL® LA 90 mg in healthy volunteers, a maximum serum concentration (Cmax) of 9.8 ± 5 ng/ml was reached after 10 hours, followed by a slow decrease (mean residence time: 26 ± 4 days, apparent half-life: 31 ± 16 days). The absolute bioavailability was 58 ± 10%.

After a single intramuscular injection of IPSTYL® LA 120 mg in healthy volunteers, a maximum serum concentration (Cmax) of 12.8 ± 7 ng/ml was reached after 16 hours, followed by a slow decrease (mean residence time: 29 ± 3 days, apparent half-life: 28 ± 6 days). The absolute bioavailability was 55 ± 10%.

Therefore lanreotide serum concentration after intramuscular administration of IPSTYL® LA 60, 90 and 120 mg shows an almost log-linear first order lanreotide release profile.

Lanreotide serum levels of 1 ng/ml are able to suppress GH to < 5 ng/ml in more than 60% of patients studied. Lanreotide serum levels of 2.5 ng/ml are able to suppress GH to < 5 ng/ml in more than 90% of patients studied.

5.3 Preclinical safety data

In vitro and animal toxicology studies have not shown any specific toxic potential for lanreotide. The observed effects are related to the pharmacological properties of lanreotide on the endocrine system.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a refrigerator between + 2°C and + 8°C in its original package. Do not freeze.

6.5 Nature and contents of container

IPSTYL® LA is supplied in a clear polypropylene pre-filled syringe with a stainless steel needle and a plunger stopper made from bromobutyl rubber coated with silicone.

Each pre-filled syringe is packed in a nylon / polyethylene / aluminium laminated bag.

Box of one individual 60mg dose in a 0.3 ml syringe with a needle (1.2 mm x 20 mm).

6.6 Instructions for use and handling

The solution for injection in a pre-filled syringe is ready for use.

For immediate and single use following first opening.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

IPSEN Limited
190 Bath Road
Slough, Berkshire
SL1 3XE, UK.

8. MARKETING AUTHORISATION NUMBER

PL 06958/0020

9. DATE OF FIRST AUTHORISATION

26 May 2004

10. DATE OF REVISION OF THE TEXT

Product Summary

1. TRADE NAME OF THE MEDICINAL PRODUCT

IPSTYL® LA 90 mg, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lanreotide (I.N.N.) 90 mg (as acetate).

For excipients, see 6.1.

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4.1 Therapeutic indications

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- Posology

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Children.
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- **Method of administration**

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Lanreotide may lead to a decrease of heart rate without necessarily reaching the threshold of bradycardia (< 60 beats per minute) in patients without an underlying cardiac problem. In patients suffering from cardiac disorders prior to lanreotide initiation, sinus bradycardia may occur and therefore heart rate should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

The gastrointestinal effects of IPSTYL® LA may reduce the intestinal absorption of co-administered drugs.

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

4.6 Pregnancy and lactation

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4.8 Undesirable effects

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Common: Hypoglycaemia or hyperglycaemia, anorexia
Uncommon: Diabetes mellitus aggravated

Nervous system disorders
Very common: Headache
Common: Dizziness

Cardiac disorders
Common: Sinus bradycardia

Gastrointestinal disorders
Very common: Diarrhoea or loose stools, abdominal pain, nausea, vomiting, dyspepsia, flatulence

Common: Constipation
Uncommon: Acute pancreatitis, steatorrhoea, tenesmus

Hepato-biliary disorders
Very common: Cholelithiasis
Common: Bilirubin increased

Skin disorders
Uncommon: Allergic skin reaction, hair loss

General disorders and administration site conditions
Common: Fatigue, Injection site reaction
Uncommon: Injection site nodule, hot flushes, somnolence, leg pain, decreased libido, increased sweating

Reactions at the injection site may occur after the deep subcutaneous injection of IPSTYL® LA in the buttock. When specific enquiry was made, pain, redness, itching and induration were reported at the injection site 30 minutes after dosing in up to 8%, 5%, 5% and 19% of patients respectively. After 3 dosing intervals, these symptoms or signs were reduced to 6%, 2% 3% and 9% of patients or fewer. In all cases, the symptoms were described as mild.

Post-marketing safety experience has not identified other relevant information. Rarely post-injection episodes of malaise with signs of dysautonomia were reported. Rare cases of persisting induration at injection site were reported.

Cardiovascular effects including a myocardial infarction (see section 4.9 Overdose), high blood pressure episodes and ventricular tachycardia have also been reported in exceptional cases with other prolonged release formulations of lanreotide.

4.9 Overdose

In clinical trials, lanreotide has been administered in doses up to 15 mg per day without serious adverse events related to the treatment. Human experience of overdose of prolonged release forms of lanreotide is limited to one unconfirmed case report of overdose where a patient was reported to have taken one intramuscular injection of the 30 mg prolonged release formulation daily for two months (instead of 1 injection every 7 to 14 days). One week after stopping therapy the 52 year-old man with a history of acromegaly, diabetes mellitus and arterial hypertension suffered a fatal cardiac infarction.

If overdosage occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigrowth hormones, ATC code: H01C B03.

Lanreotide is an octapeptide analogue of natural somatostatin. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions. It shows high binding affinity for human somatostatin receptors (SSTR) 2,

3 and 5, and reduced affinity for human SSTR 1 and 4. Activity at SSTR 2 and 5 is the primary mechanism considered to be responsible for GH inhibition.

Lanreotide, like somatostatin, exhibits a general exocrine anti-secretory action. It inhibits the basal secretion of motilin, gastric inhibitory peptide and pancreatic polypeptide, but has no significant effect on fasting secretin or gastrin secretion. Lanreotide markedly inhibits meal-induced increases in superior mesenteric artery blood flow and portal venous blood flow. Lanreotide significantly reduces prostaglandin E1-stimulated jejunal secretion of water, sodium, potassium and chloride. Lanreotide reduces prolactin levels in acromegalic patients treated long term.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lanreotide after intravenous administration in healthy volunteers indicated limited extravascular distribution, with a steady-state volume of distribution of 13 l. Total clearance was 20 l/h, terminal half-life was 2.5 hours and mean residence time was 0.68 hours.

After a single subcutaneous injection of IPSTYL® LA 60 mg in healthy volunteers, a maximum serum concentration (Cmax) 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%.

After a single intramuscular injection of IPSTYL® LA 60 mg in healthy volunteers, a maximum serum concentration (Cmax) of 6.8 ± 3 ng/ml was reached after 15 hours, followed by a slow decrease (mean residence time: 23 ± 11 days, apparent half-life: 23 ± 9 days). The absolute bioavailability was 79 ± 10%.

Therefore the route of administration (subcutaneous or intramuscular) does not show any marked influence on the lanreotide pharmacokinetic profile.

After a single intramuscular injection of IPSTYL® LA 90 mg in healthy volunteers, a maximum serum concentration (Cmax) of 9.8 ± 5 ng/ml was reached after 10 hours, followed by a slow decrease (mean residence time: 26 ± 4 days, apparent half-life: 31 ± 16 days). The absolute bioavailability was 58 ± 10%.

After a single intramuscular injection of IPSTYL® LA 120 mg in healthy volunteers, a maximum serum concentration (Cmax) of 12.8 ± 7 ng/ml was reached after 16 hours, followed by a slow decrease (mean residence time: 29 ± 3 days, apparent half-life: 28 ± 6 days). The absolute bioavailability was 55 ± 10%.

Therefore lanreotide serum concentration after intramuscular administration of IPSTYL® LA 60, 90 and 120 mg shows an almost log-linear first order lanreotide release profile.

Lanreotide serum levels of 1 ng/ml are able to suppress GH to < 5 ng/ml in more than 60% of patients studied. Lanreotide serum levels of 2.5 ng/ml are able to suppress GH to < 5 ng/ml in more than 90% of patients studied.

5.3 Preclinical safety data

In vitro and animal toxicology studies have not shown any specific toxic potential for lanreotide. The observed effects are related to the pharmacological properties of lanreotide on the endocrine system.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a refrigerator between + 2°C and + 8°C in its original package. Do not freeze.

6.5 Nature and contents of container

IPSTYL® LA is supplied in a clear polypropylene pre-filled syringe with a stainless steel needle and a plunger stopper made from bromobutyl rubber coated with silicone.

Each pre-filled syringe is packed in a nylon / polyethylene / aluminium laminated bag.

Box of one individual 90mg dose in a 0.3 ml syringe with a needle (1.2 mm x 20 mm).

6.6 Instructions for use and handling

The solution for injection in a pre-filled syringe is ready for use.

For immediate and single use following first opening.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

IPSEN Limited
190 Bath Road
Slough, Berkshire
SL1 3XE, UK.

8. MARKETING AUTHORISATION NUMBER

PL 06958/0021

9. DATE OF FIRST AUTHORISATION

26 May 2004

10. DATE OF REVISION OF THE TEXT

Product Summary

1. TRADE NAME OF THE MEDICINAL PRODUCT

IPSTYL® 120 mg, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lanreotide (I.N.N.) 120 mg (as acetate).

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

White to off-white, translucent and viscous supersaturated solution in a pre-filled syringe, ready for use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IPSTYL® LA 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 goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalise these values.

4.2 Posology and method of administration

- Posology

In patients receiving a somatostatin analogue for the first time, the recommended starting dose is 60 mg of IPSTYL® LA administered every 28 days.

Thereafter, for all patients, 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 IGF1 levels).

If the desired response is not obtained, the dose may be increased.

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.

Long term monitoring of symptoms, GH and IGF1 levels should be undertaken as clinically indicated.

Hepatic/renal impairment and the elderly.

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 hepatic impairment, an increase in volume of distribution and mean residence time is observed, but there is no difference in total clearance or AUC. Elderly subjects show an increase in half-life and mean residence time compared with healthy young subjects. Due to the wide therapeutic window of lanreotide, it is not necessary to alter the dose in these circumstances.

Children.
Currently there is no experience of administration of IPSTYL® LA in children, therefore use of IPSTYL® LA in children cannot be recommended.

- **Method of administration**

IPSTYL® LA should be injected via the deep sub-cutaneous route in the superior external quadrant of the buttock. The skin should not be folded. The needle should be inserted rapidly to its full length, perpendicularly to the skin.

4.3 Contra-indications

Hypersensitivity to lanreotide or related peptides.

4.4 Special warnings and precautions for use

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and its analogues, inhibits the secretion of insulin and glucagon. Hence, patients treated with IPSTYL® LA may experience hypoglycaemia or hyperglycaemia. Blood glucose levels should monitored when lanreotide treatment is initiated and treatment of diabetic patients should be accordingly adjusted. In insulin-dependent patients, insulin requirements may be reduced.

Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, although clinical hypothyroidism is rare (<1%). Tests of thyroid function should be done where clinically indicated.

Lanreotide may reduce gall bladder motility and gall bladder ultrasonography is therefore advised at the start of treatment and periodically thereafter. If gallstones do occur, they are generally asymptomatic. Symptomatic stones should be treated as medically indicated.

Lanreotide may lead to a decrease of heart rate without necessarily reaching the threshold of bradycardia (< 60 beats per minute) in patients without an underlying

cardiac problem. In patients suffering from cardiac disorders prior to lanreotide initiation, sinus bradycardia may occur and therefore heart rate should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

The gastrointestinal effects of IPSTYL® LA may reduce the intestinal absorption of co-administered drugs.

Concomitant administration of lanreotide injection with cyclosporin may decrease blood levels of cyclosporin, hence blood levels of cyclosporin should be monitored.

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

4.6 Pregnancy and lactation

Reproductive studies in rats and rabbits at doses up to 33 times the human dose have failed to demonstrate a risk to the foetus; however there are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used in pregnant or breast-feeding women only if clearly needed.

Eleven pregnancies have been reported in patients who were being treated with lanreotide. Ten cases originated from patients with acromegaly and 1 case from a patient with neuroendocrine tumours. In five cases (four patients with acromegaly and one patient with neuroendocrine tumours) the course and outcome of the pregnancy were normal. In one case the outcome was a premature delivery, however, this patient suffered from arterial hypertension and she underwent pituitary surgery during pregnancy. In one case the patient decided to abort. The four remaining cases resulted in a miscarriage, however two of these cases were poorly documented and in no case could a causal relationship to lanreotide treatment be established.

4.7 Effects on ability to drive and use machines

No effects of IPSTYL® LA on ability to drive and use machines have been described.

4.8 Undesirable effects

The adverse reactions related to IPSTYL® LA during clinical trials are consistent with those seen with other prolonged release formulations of lanreotide, and are predominantly gastrointestinal. The most commonly reported adverse reactions in clinical trials are diarrhoea, abdominal pain, nausea, vomiting, dyspepsia, flatulence, cholelithiasis and headache. These reactions are usually mild and transient.

Undesirable effects are listed under the corresponding body organ systems according to the following classification: Very common >10%; common >1.0% to < 10%; uncommon > 0.1% to < 1.0%.

Metabolism and nutrition disorders
Common: Hypoglycaemia or hyperglycaemia, anorexia
Uncommon: Diabetes mellitus aggravated

Nervous system disorders
Very common: Headache
Common: Dizziness

Cardiac disorders
Common: Sinus bradycardia

Gastrointestinal disorders
Very common: Diarrhoea or loose stools, abdominal pain, nausea, vomiting, dyspepsia, flatulence
Common: Constipation
Uncommon: Acute pancreatitis, steatorrhoea, tenesmus

Hepato-biliary disorders
Very common: Cholelithiasis
Common: Bilirubin increased

Skin disorders
Uncommon: Allergic skin reaction, hair loss

General disorders and administration site conditions
Common: Fatigue, Injection site reaction
Uncommon: Injection site nodule, hot flushes, somnolence, leg pain, decreased libido, increased sweating

Reactions at the injection site may occur after the deep subcutaneous injection of IPSTYL® LA in the buttock. When specific enquiry was made, pain, redness, itching and induration were reported at the injection site 30 minutes after dosing in up to 8%, 5%, 5% and 19% of patients respectively. After 3 dosing intervals, these symptoms or signs were reduced to 6%, 2% 3% and 9% of patients or fewer. In all cases, the symptoms were described as mild.

Post-marketing safety experience has not identified other relevant information. Rarely post-injection episodes of malaise with signs of dysautonomia were reported. Rare cases of persisting induration at injection site were reported.

Cardiovascular effects including a myocardial infarction (see section 4.9 Overdose), high blood pressure episodes and ventricular tachycardia have also been reported in exceptional cases with other prolonged release formulations of lanreotide.

4.9 Overdose

In clinical trials, lanreotide has been administered in doses up to 15 mg per day without serious adverse events related to the treatment. Human experience of overdose of prolonged release forms of lanreotide is limited to one unconfirmed case report of overdose where a patient was reported to have taken one intramuscular injection of the 30 mg prolonged release formulation daily for two months (instead of 1 injection every 7 to 14 days). One week after stopping therapy the 52 year-old man with a history of acromegaly, diabetes mellitus and arterial hypertension suffered a fatal cardiac infarction.

If overdosage occurs, symptomatic management is indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antigrowth hormones, ATC code: H01C B03.

Lanreotide is an octapeptide analogue of natural somatostatin. Like somatostatin, lanreotide is an inhibitor of various endocrine, neuroendocrine, exocrine and paracrine functions. It shows high binding affinity for human somatostatin receptors (SSTR) 2, 3 and 5, and reduced affinity for human SSTR 1 and 4. Activity at SSTR 2 and 5 is the primary mechanism considered to be responsible for GH inhibition.

Lanreotide, like somatostatin, exhibits a general exocrine anti-secretory action. It inhibits the basal secretion of motilin, gastric inhibitory peptide and pancreatic polypeptide, but has no significant effect on fasting secretin or gastrin secretion. Lanreotide markedly inhibits meal-induced increases in superior mesenteric artery blood flow and portal venous blood flow. Lanreotide significantly reduces prostaglandin E1-stimulated jejunal secretion of water, sodium, potassium and chloride. Lanreotide reduces prolactin levels in acromegalic patients treated long term.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of lanreotide after intravenous administration in healthy volunteers indicated limited extravascular distribution, with a steady-state volume of distribution of 13 l. Total clearance was 20 l/h, terminal half-life was 2.5 hours and mean residence time was 0.68 hours.

After a single subcutaneous injection of IPSTYL® LA 60 mg in healthy volunteers, a maximum serum concentration (Cmax) 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%.

After a single intramuscular injection of IPSTYL® LA 60 mg in healthy volunteers, a maximum serum concentration (Cmax) of 6.8 ± 3 ng/ml was reached after 15 hours, followed by a slow decrease (mean residence time: 23 ± 11 days, apparent half-life: 23 ± 9 days). The absolute bioavailability was 79 ± 10%.

Therefore the route of administration (subcutaneous or intramuscular) does not show any marked influence on the lanreotide pharmacokinetic profile.

After a single intramuscular injection of IPSTYL® LA 90 mg in healthy volunteers, a maximum serum concentration (Cmax) of 9.8 ± 5 ng/ml was reached after 10 hours, followed by a slow decrease (mean residence time: 26 ± 4 days, apparent half-life: 31 ± 16 days). The absolute bioavailability was 58 ± 10%.

After a single intramuscular injection of IPSTYL® LA 120 mg in healthy volunteers, a maximum serum concentration (Cmax) of 12.8 ± 7 ng/ml was reached after 16 hours, followed by a slow decrease (mean residence time: 29 ± 3 days, apparent half-life: 28 ± 6 days). The absolute bioavailability was 55 ± 10%.

Therefore lanreotide serum concentration after intramuscular administration of IPSTYL® LA 60, 90 and 120 mg shows an almost log-linear first order lanreotide release profile.

Lanreotide serum levels of 1 ng/ml are able to suppress GH to < 5 ng/ml in more than 60% of patients studied. Lanreotide serum levels of 2.5 ng/ml are able to suppress GH to < 5 ng/ml in more than 90% of patients studied.

5.3 Preclinical safety data

In vitro and animal toxicology studies have not shown any specific toxic potential for lanreotide. The observed effects are related to the pharmacological properties of lanreotide on the endocrine system.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a refrigerator between + 2°C and + 8°C in its original package. Do not freeze.

6.5 Nature and contents of container

IPSTYL® LA is supplied in a clear polypropylene pre-filled syringe with a stainless steel needle and a plunger stopper made from bromobutyl rubber coated with silicone.

Each pre-filled syringe is packed in a nylon / polyethylene / aluminium laminated bag.

Box of one individual 120 mg dose in a 0.5 ml syringe with a needle (1.4 mm x 20mm).

6.6 Instructions for use and handling

The solution for injection in a pre-filled syringe is ready for use.

For immediate and single use following first opening.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

IPSEN Limited
190 Bath Road
Slough, Berkshire
SL1 3XE, UK.

8. MARKETING AUTHORISATION NUMBER

PL 06958/0022

9. DATE OF FIRST AUTHORISATION

26 May 2004

10. DATE OF REVISION OF THE TEXT

OUTSTANDING ISSUES

There are no outstanding issues.

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

MODULE 3 - QUALITY PHARMACEUTICAL ASSESSMENT

Assessment Report
Mutual recognition Procedure

Ipstyl LA 60, 90, 120mg Solution for Injection

Lanreotide Acetate

UK/H/0723/001-003

Applicant: Ipsen Ltd

Date: 15th October 2004

TABLE OF CONTENTS

MODULE 3 - QUALITY
PHARMACEUTICAL ASSESSMENT

UK LICENCE No.:	**PL 06958/0020-22**
PRODUCT:	**Ipstyl LA 60, 90 and 120mg Solution for Injection**
ACTIVE(S):	**Lanreotide Acetate**
COMPANY:	**Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK**
EC ARTICLE:	**Full dossier, Article 8.3(i)**

IV.1

I. REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

None Required. Satisfactory inspection reports have been provided for the active substance manufacturer and authorisations for the drug product manufacturers.

II. INTRODUCTION

These applications are updated, duplicate licences to the already authorised products: Somatuline Autogel 60, 90 & 120 mg (PL 06958/0013-15). The Somatuline Autogel products were themselves, line extensions of PL 06958/0018 (Somatuline LA injection), which was the first lanreotide application in the EEA. The Ipstyl LA applications are therefore, line extensions of Somatuline LA (PL 06958/0018), however, a full dossier has been provided for all Modules. This approach has been taken since the MAH intends to start a Mutual Recognition Procedure and not all Concerned Member States have granted a Marketing Authorisation for the original Somatuline LA (PL 06958/0018). Somatuline LA injection is formulated in poly- lactide / glycolide (PLG) microspheres in order to achieve prolonged release over 14 days, with an initial loading of 30 mg lanreotide. {Somatuline LA injection may be given in repeat doses on day 7, 10 or 14 following previous injection, depending on the response of the individual patient.}

Lanreotide is a chemically synthesised analogue of somatostatin, which is a growth hormone inhibitor. The product is indicated for the treatment of acromegaly.

The current applications apply for three formulation strengths in the pharmaceutical form: solution for injection, to be delivered by deep sub-cutaneous route of administration. Rather than using the controlled hydrolysis of the PLG microspheres as is the case for Somatuline LA, the prolonged release effect is achieved by use of a highly concentrated (supersaturated) solution which results in a gel forming following injection and gradual dissolution occurs into the systemic circulation. The three strengths (60/90/120 mg) are proposed to be given every 28 days and the effects stated to be equivalent to the current product (30 mg) given every 14, 10 or 7 days respectively.

The legal base is that of a full dossier, i.e. 2001/83/EC Article 8.3(i).

III. DRUG SUBSTANCE

IV.1.1 III.1 General Information

The drug substance is an octapeptide, containing a disulphide bond between the two cysteine residues and the D- forms of both β-Nal and Trp.

IV.1.2 III.2 Nomenclature

Lanreotide (INN) acetate.

IV.1.3 III.3 Structure

[cyclo S-S]-3-(2-naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide acetate.

$C_{54}H_{69}N_{11}O_{10}S_2 (CH_3COOH)_x$, where x = 1.6 to 3.2

IV.1.4 III.4 General properties

The optical rotation, $[\alpha]^{26}_D$ of lanreotide has been determined as –90.88 ° ± 2.94%. [redacted]

The solubility of the drug has been studied and shown to be a maximum at pH 5.02 with a value of 37.6 g/l. [redacted] Redacted according to Section 43, FOI Act

[redacted]

IV.1.5 III.5 Manufacture

IV.2

IV.2.1.1 *III.5.1 Manufacturer*

Lanreotide acetate is manufactured and released by:

[redacted] Redacted according to Section 43, FOI Act

Satisfactory GMP inspections have been performed on this site; see covering letter from Irish Medicines Board of 15-Oct-2003 regarding IMB inspection on 7th October 2003.

IV.2.1.2 *III.5.2 Description of process and controls*

[redacted]

Redacted according to Section 43, FOI Act

[redacted] Redacted according to Section 43, FOI Act

IV.2.1.3 ***III.5.3 Control of materials***

[redacted]

Specifications have also been provided for reagents, solvents. [redacted]

IV.2.1.4 ***III.5.4 Control Critical Steps and Intermediates***

Critical steps are as follows:

[redacted]

IV.2.1.5 ***III.5.5 Process validation***

The process is stated to be validated as a result of the application of the in-process controls described in the previous Section (III.5.4) which results in a consistent process and yields. This is supported by batch analysis data for [redacted] lots manufactured in [redacted]. Consistency of the manufacturing process is supported by validation data for four representative lots of drug substance.

IV.2.1.6 ***III.5.6 Manufacturing process development***

[redacted]

IV.2.2 III.6 Characterisation

IV.2.2.1 *III.6.1 Elucidation of Structure and other characteristics*

Proof of structure comprised the following techniques: [redacted]

Redacted according to Section 43, FOI Act

These tests are satisfactory and the validation of the analytical methods shows their suitability.

IV.2.2.2 *III.6.2 Impurities*

Related peptide substances considered likely to be present are as follows [redacted]

IV.2.3 III.7 Control of Drug Substance

The specifications applied at the Drug substance Manufacturing Site are as follows:

Redacted according to Section 43, FOI Act

*CFU = Colony Forming Units.

Satisfactory methods and validations for other tests have been provided.

IV.2.4 III.8 Reference Standards or Materials

The primary reference standard for lanreotide acetate is

[redacted] Batch data for the primary standard have been provided. Batch data and Certificate of Analysis for the working standard, [redacted] has also been provided.

Redacted according to Section 43, FOI Act

IV.2.5 III.9 Container Closure System

The drug substance is packed in [redacted]

[redacted]

IV.2.6 III.10 Stability

[redacted] production batches manufactured by [redacted] were placed on stability [redacted]

[redacted]

[redacted]

[redacted]

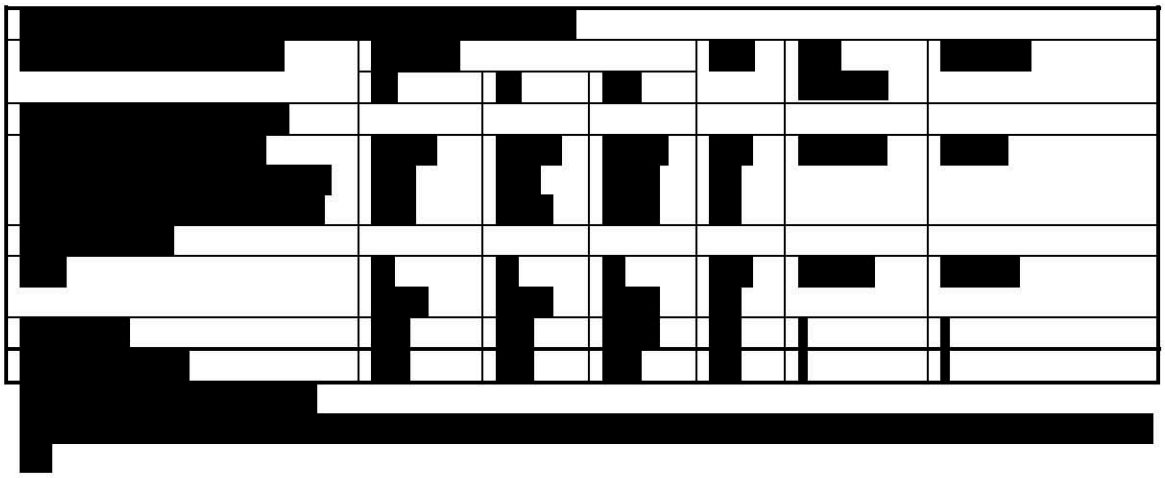
[redacted]

Based on the stability data provided, a retest period of 24 months is proposed for the drug substance when stored at 5 ± 3 °C. This proposal is acceptable.

IV. DRUG PRODUCT

IV.2.7 IV.1 Description and Composition of the Drug Product

The composition of the product is as follows:



Redacted according to Section 43, FOI Act

The composition of the product is very simple and presents no issues.

IV.2.8 IV.2 Pharmaceutical Development

[redacted]

Redacted according to Section 43, FOI Act

[redacted]

Redacted according to Section 43, FOI Act

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Redacted according to Section 43, FOI Act

IV.2.9 IV.3 Manufacture

[redacted]

IV.2.10 IV.4 Process

[redacted]

[redacted]

Redacted according to Section 43, FOI Act

Flow charts for the [redacted] and manufacturing process have been provided and are acceptable.

In-process controls (IPC's)
Satisfactory IPC's have been described for the [redacted]

IV.2.11 IV.5 Validation

[redacted]

[redacted]

Redacted according to Section 43, FOI Act

IV.2.12 IV.6 TSE

The excipient, WFI (see IV.4) is not of concern regarding TSE.

The only other material in the product is the drug substance, composed of amino acids. A contractual agreement is in place between the manufacturer of the drug substance [redacted] and their suppliers in order to ensure that amino acids are not from bovine, ovine or caprine origin (most are from poultry and fish, one is sourced from human hair). A copy of this agreement has been provided.

IV.2.13 IV.7 Control of Excipients

The only excipent present in the product is Water for Injections, meeting the requirements of the Ph. Eur., see under composition.

IV.2.14 IV.8 Control of Drug Product

Product is tested to the following comprehensive in-house specification on release.

[redacted]		
[redacted]		
[redacted]		

*This test is not performed routinely but is replaced by parametric release

Satisfactory descriptions of the analytical methods have been provided.

Satisfactory justification of the proposed limits has been provided.

Analytical validation
Satisfactory validation reports have been provided for the non-pharmacopoeial methods.

Batch data

[redacted]

Batch data for [redacted] lots of 60 / 90 / 120 mg product have been provided and are satisfactory.

IV.2.15 IV.9 Reference Standards or Materials

Working reference standards for lanreotide was batch [redacted], see Section III.8 also.

[redacted]

IV.2.16 IV.10 Container Closure System

The primary package is a gamma resistant 0.3 or 0.5 mL polypropylene syringe [redacted]. This is siliconised [redacted] and fitted with bromobutyl rubber plunger [redacted], also siliconised [redacted]. The needles (1.2 or 1.4 mm x 20 mm) are of stainless steel 304 ([redacted]) and protected with a rubber needle sheath ([redacted]). The siliconised syringes are supplied by [redacted].

[redacted]

Satisfactory specifications for [redacted] and other packaging components have been provided.

Plunger stoppers are [redacted] grey and meet the requirements of Ph. Eur. 3.1.12 (rubber closures for parenteral products).

Needles are manufactured to dimensional and ISO 7864 specifications ([redacted]).

Needle sheaths are manufactured to ISO 8871 specifications ([redacted]). Redacted according to Section 43, FOI Act

[redacted]

Satisfactory analysis of needle and syringe bonding forces has been demonstrated.

The secondary packaging is composed of an additional finger grip to aid expulsion of the formulation and a cylindrical plunger protector composed of acrylonitrile butadiene styrene and polycarbonate. The finished product is placed in an outer wrapper composed of aluminium, nylon and polyethylene prior to gamma sterilisation. Specifications for the secondary packaging are satisfactory.

Biocompatibility testing has been performed on non-irradiated and 38 kGy irradiated polypropylene and meets the requirements of USP <87> (Biological Reactivity *in-vitro*), USP <88> (Biological Reactivity *in-vivo*) and USP <661> (Physicochemical tests - plastics). A report on the biocompatibility of the siliconised syringes has been provided and is satisfactory from pharmaceutical perspective.

IV.2.17 **IV.11 Stability**

The following batches have been evaluated during stability testing of the finished product:

[redacted]

The product was checked against the finished product specification, [redacted]

All tests were within the required specification and little additional degradation was observed, [redacted]

No evidence of extractables was found in the batches treated with a range of irradiation doses and stored for up to [redacted].

[redacted] Redacted according to Section 43, FOI Act

The proposed shelf life of 2 years at 2 – 8 °C is satisfactory.

V. APPENDICES

None

VI. REGIONAL INFORMATION

National MAA and product literature included.

VII. ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Summary of Product Characteristics

None

Patient Information Leaflet

Generally satisfactory, a commercial mock-up has been provided.

Label

Satisfactory, commercial mock-ups have been provided.

VIII. ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

The dossier is generally satisfactory.

[redacted] Redacted according to Section 40, FOI Act

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

MODULE 4
NON-CLINICAL ASSESSMENT

Assessment Report
Mutual recognition Procedure

Ipstyl LA 60, 90, 120mg Solution for Injection

Lanreotide Acetate

UK/H/0723/001-003

Applicant: Ipsen Ltd

Date: <Date report completed>

TABLE OF CONTENTS

MODULE 4
NON-CLINICAL ASSESSMENT

UK LICENCE No.:	**PL 06958/0020-22**
PRODUCT:	**Ipstyl LA 60, 90 and 120mg Solution for Injection**
ACTIVE(S):	**Lanreotide Acetate**
COMPANY:	**Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK**
EC ARTICLE:	**Full dossier, Article 8.3(i)**

IV.3 I INTRODUCTION

Ipsen Limited is applying for a Marketing Authorisation for Ipstyl LA. These applications relate to products identical to ones currently approved in the UK - Somatuline Autogel 60mg, 90mg & 120mg (PL 06958/0013-0015). The applications for the latter were abridged line extensions of another UK approved product, Somatuline LA (PL 06958/0018). These present UK applications for Ipstyl LA are being submitted solely to support the mutual recognition in Germany. Ipsen Limited does not plan to market product against these licenses in the UK, it will continue to market Somatuline Autogel as currently approved. The Somatuline LA product on which the original UK line extension application for Somatuline Autogel was based is not approved in Germany. Therefore, the Company has prepared this stand-alone dossier combining the data from Somatuline LA and Somatuline Autogel.

Authorisation is sought to market Ipstyl LA as a treatment for acromegaly, when the secretion of growth hormones is not normalised after surgery and/or radiation therapy. The anticipated clinical dosing regimen is one deep s.c. injection of Ipstyl LA 60, 90 or 120mg every 28 days, in adults, using a formulation that contains lanreotide base 0.246 mg/mg of solution. Lanreotide is a synthetic octapeptide analogue of natural somatostatin with structural modifications intended to increase resistance to enzymatic degradation and thus prolong plasma half-life and to reduce binding to central nervous system receptors.

The stand-alone dossier also includes some preclinical data not previously submitted. The Applicant has submitted a table listing the new studies. Since the application relates to a product identical to one currently approved in the UK, the entire non-clinical data will not be re-assessed in detail. The applicant's non-clinical overview provides an adequate summary of the pharmacotoxicology of the active ingredient. Only the new studies will be considered in detail.

IV.4 II PHARMACOLOGY

IV.4.1 II.1 Primary pharmacodynamics

In a non-GLP study, prolonged release Somatuline administered at 2mg/kg/10d over a one-month period elicited a decrease in the anterior pituitary weight and in the plasma levels of prolactin in oestrogenised rats presenting both a hyperprolactinaemia and a hyperplasia of prolactin cells.

IV.4.2 II.2 Secondary Pharmacodynamics

No new data.

IV.4.3 II.3 Safety Pharmacology

Lanreotide acetate prolonged release formulation 30mg administered to conscious dogs by the intramuscular route at single doses of 0.43 or 4.3 mg/kg elicited no toxicologically significant effect on anterial blood pressure, heart rate, PR, QT and QTc interval duration and QRS complex. There were no effects on the ECG and no overt signs of toxicity over a 14-day post-dose period.

IV.5 III PHARMACOKINETICS

IV.5.1 III.1 Absorption

Lanreotide acetate administered to rats by the subcutaneous route in a repeated dose regimen (40, 100, 1000 mg/kg/12hr) for 6 days gave steady state values of 1.7, 3.7 and 48.2 ng/ml respectively, indicating pharmacokinetic linearity over the dose range tested.

Lanreotide acetate administered to dogs by the s.c. route in a repeated dose regimen (80, 200 or 2000ug/kg/day) revealed linear pharmacokinetics over the dose range tested. Linear pharmacokinetics were also demonstrated in the dogs following i.v. infusion over 24 hours at dose levels of 50, 100 or 200ug/hr.

In another study in the rat, linear pharmacokinetics were demonstrated following single i.v. or s.c. doses at 80 and 200ug/kg. The bioavailability by the s.c. route was 67% and 75% at 80 and 200ug/kg respectively.

IV.5.2 III.2 Distribution

Following a single i.v. or s.c. dose of ^{14}C-lanreotide at 2mg/kg to pigmented or albino rats, the distribution of radioactivity was similar following either route of administration. The data indicated that the dose was well, but slowly, absorbed from the s.c. injection site. Highest concentrations of radioactivity generally occurred at 8 hours and 24 hours after s.c. and i.v. administration respectively. The highest concentrations of radioactivity were in the pancreas with high levels at all times generally occurred in glandular tissue. Radioactivity remained widely distributed at 168 hours following each administration route which indicated that the

site of radiolabelling was metabolically unstable and radiolabelled carbon has been incorporated into normal body processes. High levels of radioactivity in the gastrointestinal tract was consistent with biliary secretion. Melanin binding of radiolabelled component was not significant.

IV.5.3 III.3 Metabolism

A study was conducted in rats to determine the metabolic profile in plasma, bile, urine and faeces following i.v. and s.c. administration of (1-^{14}C-Val^{6}) - lanreotide at 1000ug/kg. Previous results may have been affected by in vivo chemical instability of the radiolabel. Radiolabelled lanreotide was extensively metabolised to CO_2 and most probably to numerous peptide fragments and other breakdown products. Unchanged lanreotide was the major component excreted in bile. One metabolite (P-18.2) accounting for 10.9 and 2.9% of the dose after s.c. and i.v. administration respectively was tentatively identified as Des-Thr-lanreotide. In general all other metabolites were of a minor nature. The applicant speculated that degradation of biliary secreted lanreotide and its metabolites most likely occurred in the gut presumably by microbial flora and/or host proteases, followed by re-absorption of some drug related material. The applicant speculated that a significant proportion of the applied radioactivity was incorporated into normal body processes.

A study was conducted in dogs to determine the metabolism of (1-^{14}C-Val^{6})-lanreotide following i.v. or s.c. administration. About 25% were extensively metabolised. Unchanged lanreotide was the major component excreted in urine and faeces. However, one not chemically identified metabolite (p-37.0) accounting for 34% of the dose after i.v. administration was the most abundant radioactive component secreted in bile. All other metabolites in bile, plasma, urine and faeces were of a minor nature and these were little differences in metabolic profiles following either route of administration.

IV.5.4 III.4 Excretion

The biliary excretion of radioactivity in male bile duct cannulated dogs following a single i.v. dose of ^{14}C - lanreotide at 0.2 mg/kg was approximately 28% of the administered dose.

Studies in rats and dogs revealed that following s.c. or i.v. administration of ^{14}C - lanreotide, the site of radiolobelling was metabolically unstable.

IV.6 IV TOXICOLOGY

IV.6.1 IV.1 Repeated dose toxicology

Sections of testes from a 45-day i.v. infusion study in Beagle dogs were peer reviewed. The treatment regimen was 0, 0.4, 4 or 10 mg/kg/day continuous injections of lanreotide acetate to 4 dogs/sex/group. “Immature” testes were recorded in all dogs at 10mg/kg and in one dog at 4mg/kg. The findings were stated to be consistent with withdrawal of the trophic influence of testosterone rather than a direct toxic effect on the testes, although the absence of associated changes in the prostate and pituitary gland were unusual in this regard. Reduction of body weight gain may have also contributed in part to the delay of sexual maturation.

The toxicity of lanreotide was investigated in rats and dogs in 5 studies: 6 weeks duration in dogs and rats by the s.c. route; in dogs by continuous infusion over 45 days; 26 week study in dogs involving bi-monthly administration of a prolonged – release pharmaceutical form; a 15-week study in rats involving twice-daily s.c. injection of an immediate release pharmaceutical form. The assay of hormones revealed no effects on insulin, thyroxine or testosterone except in the continuous infusion study in dogs in which secretion of glucagon thyroxine and testosterone were decreased. This finding was attributed to the high dose levels administered. The 15-week rat study and 26 week dog study revealed an inhibitory effect on growth hormone (GH) production. This inhibition was brief (8 days), non-cumulative, and reversible (8 days) after cessation of treatment.

IV.6.2 IV.2 Genotoxicity

A full package of studies with lanreotide acetate were conducted. All the studies were GLP-compliant.

Lanreotide acetate did not induce mutation in four strains (TA98, TA100, TA1535 and TA1537) of S. typhimurium and one strain (WP2uvrA) of E.coli at concentrations ranging from 20.48 to 5000ug/plate (a toxic and precipitating dose level) in the presence and absence of metabolic activation.

Lanreotide acetate did not induce mutation when tested at up to toxic and precipitating dose levels (100-1200ug/ml) at the tk locus of L5178Y lymphoma cells in the presence and absence of metabolic activation.

Lanreotide acetate did not induce chromosome aberrations in cultured human peripheral blood lymphocytes when tested to the limit of solubility (3+17 hours) without metabolic activation or the limit of cytotoxicity (3+17 hours with metabolic activation or 20+0 hours without metabolic activation).

In a bone marrow micronucleas test, lanreotide acetate was not clastogenic in mice bone marrow cells after two i.v. administrations at dose levels of 6.25, 12.5 or 25mg/kg/day at a 24 hour interval.

IV.6.3 IV.3 Reproductive And Developmental Toxicity

A rat segment I study was conducted at dose levels of 200, 600 or 2000ug/kg/day administered by twice daily s.c. injection. All 3 dose levels resulted in toxicity to male rats, characterised by a progressive reduction in body weight gain. A similar effect occurred in females at 600 and 2000ug/kg. Fertility and mating performance were not affected at any dose level except for slightly reduced litter sizes at 600 and 1200ug/kg, resulting from lower numbers of corpora lutea in association with the reduced maternal body weight. There were no lasting effects on the development and reproductive capacity of the F1 generation at any dose level.

IV.7 V ENVIRONMENTAL RISK ASSESSMENT

An ERA has shown that the therapeutic use of lanreotide presents no risk to the environment.

IV.8 VI NON-CLINICAL OVERVIEW

The non-clinical overview was written by [redacted] a suitably qualified toxicologist and independent consultant. It provides a satisfactory overview and critical appraisal of the data.

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IV.9 VII SmPC

Section 5.3 of the SmPC is acceptable.

IV.10VIII CONCLUSION

The results of the new data have not raised any concerns of toxicological significance. The data supports the conclusion that the product can be safely used in its proposed therapeutic indication.

[redacted]

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December 2003

MODULE 5
CLINICAL ASSESSMENT

Assessment Report
Mutual recognition Procedure

Ipstyl LA 60, 90, 120mg Solution for Injection

Lanreotide Acetate

UK/H/0723/001-003

Applicant: Ipsen Ltd

Date: 15th October 2004

TABLE OF CONTENTS

MODULE 5
CLINICAL ASSESSMENT

UK LICENCE No.:	**PL 06958/0020-22**
PRODUCT:	**Ipstyl LA 60, 90 and 120mg Solution for Injection**
ACTIVE(S):	**Lanreotide Acetate**
COMPANY:	**Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK**
EC ARTICLE:	**Full dossier, Article 8.3(i)**

I. INTRODUCTION

Lanreotide Microparticles has been registered and supplied in over 40 countries and has demonstrated an acceptable efficacy and safety profile in clinical use. The new formulation of lanreotide Autogel has shown similar qualities in clinical trials.

The development of this new preparation had the objective of extending the duration of the release of the active ingredient and obtaining a fixed time interval of 28 days between each injection. The supersaturated solution contains only lanreotide and water.

The clinical development of this new formulation of lanreotide was based on three logical development stages. Firstly, an analysis of existing data was used to establish a relationship between the pharmacokinetics of lanreotide and the response of the biomedical marker, Growth Hormone (GH). This allowed for a target serum level of lanreotide to be established.

Secondly, the pharmacokinetics of the new Autogel formulation were determined at a series of different lanreotide concentrations and by the intramuscular and subcutaneous routes, at a number of injection sites. This second stage allowed for the preferred formulation, route and site of injection to be chosen.

Finally, the clinical efficacy and safety of the chosen Autogel formulations by the chosen administration route were defined in two pivotal studies. The first of the two pivotal studies [redacted] evaluated the efficacy of three repeated deep subcutaneous administrations of lanreotide Autogel (60, 90 or 120mg) at fixed dosed in acromegalic patients previously treated with the lanreotide 30mg microparticle formulation. Included in this study were determinations of serum lanreotide level at trough, allowing confirmation that target lanreotide levels were consistently being achieved in the patient population.

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This study showed lanreotide Autogel to be no less effective than lanreotide Microparticles in maintaining GH levels and in controlling IGF-1. Over a 12-month period, treatment was

associated with further improvements both in biological and clinical indicators of the acromegaly disease.

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The second pivotal lanreotide Autogel study ([redacted]) recruited patients who completed the first and demonstrates the longer-term efficacy and safety of lanreotide Autogel in acromegalics. Furthermore, since a relationship between trough lanreotide serum levels and GH response has been established, three key and seven supportive clinical efficacy studies conducted with the lanreotide microparticle formulation are presented as further evidence that lanreotide is effective in the treatment of acromegaly when delivered to the patient within an appropriate plasma concentration range.

The pharmacological properties of lanreotide have been linked to a high incidence of gastrointestinal AEs, and the profile of gastrointestinal adverse events seen with lanreotide Autogel was very similar to that seen with lanreotide Microparticles.

Taken together the data clearly support the safety and efficacy of lanreotide Autogel in the treatment of acromegaly when the circulating levels of growth hormone remain abnormal after surgery and/or radiotherapy or in patients who otherwise require medical treatment.

In summary, lanreotide Autogel offers advantages for the clinician (longer duration of action, ready for use injection) and for the patient (reduced frequency of injection, deep subcutaneous injection). Like lanreotide Microparticles, lanreotide Autogel provides distinct improvement in the symptoms of acromegaly and has demonstrated a safety profile that is encouragingly acceptable in relation to the risk/benefit ratio. The advantages of this ready to use formulation make it a significant addition to the treatments available for patients suffering from active acromegaly, in particular those patients who have failed to respond to optimal therapy with surgery and/or radiotherapy.

II. INDICATIONS

IPSTYL® LA 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 goal of treatment in acromegaly is to reduce GH and IGF-1 levels and where possible to normalise these values.

III. DOSE & DOSE SCHEDULE

In patients receiving a somatostatin analogue for the first time, the recommended starting dose is 60 mg of IPSTYL® LA administered every 28 days. Thereafter, for all patients, 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 IGF1 levels).

If the desired response is not obtained, the dose may be increased. 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.

Long term monitoring of symptoms, GH and IGF1 levels should be undertaken as clinically indicated.

Hepatic/renal impairment and the elderly.

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 hepatic impairment, an increase in volume of distribution and mean residence time are observed, but there is no difference in total clearance or AUC. Elderly subjects show an increase in half-life and mean residence time compared with healthy young subjects. Due to the wide therapeutic window of lanreotide, it is not necessary to alter the dose in these circumstances.

Children.

Currently there is no experience of administration of IPSTYL® LA in children, therefore use of IPSTYL® LA in children cannot be recommended.

Method of administration

IPSTYL® LA should be injected via the deep sub-cutaneous route in the superior external quadrant of the buttock. The skin should not be folded. The needle should be inserted rapidly to its full length, perpendicularly to the skin.

IV. OVERVIEW OF BIOPHARMACEUTICS

IV.10.1 IV.1 Pharmacokinetic studies performed during lanreotide Autogel development

Pharmacokinetic studies conducted in healthy volunteers were used during development of lanreotide Autogel in order to optimise the formulation and route of administration for the product. Different concentrations (0.205 mg/mg, 0.246 mg/mg, 0.287 mg/mg) and dosages (20, 30, 40, 60, 90, 120mg) of lanreotide Autogel were administered by i.m., s.c. or deep s.c. routes at a number of injection sites and compared during the course of these studies ([redacted]). The pharmacokinetic profile was studies by comparing the pharmacokinetic parameters of lanreotide Autogel to those of lanreotide IRF and lanreotide microparticle formulations.

Redacted according to Section 40, FOI Act

The results of these single dose studies in healthy volunteers allow the following conclusions:

1) The absolute bioavailability of lanreotide Autogel is approximately 60 to 70% and the terminal half life is approximately 4 weeks.

2) The relative bioavailability of lanreotide Autogel compared to the immediate release s.c. form is about 80 to 90%.

3) A linear pharmacokinetic behaviour of lanreotide Autogel was observed in the studied dose range

4) The s.c. administration of lanreotide Autogel allows a better sustained release of lanreotide than the i.m. administration of the microparticles allowing a less acute initial exposure and a more constant drug release over time.

5) In healthy volunteers, the lanreotide levels observed after administration of lanreotide Autogel (i.m. and s.c. route) are compatible with its use as a monthly dosing formulation.

6) On the basis of the pharmacokinetic study results, the 0.246 mg/ mg formulation of lanreotide Autogel was the optimum candidate for further development at doses of 60, 90 and 120 mg over a 28 day period. This equates to the same monthly dose of lanreotide as established for the 30mg Microparticle formulation given every 14, 10 or 7 days.

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Lanreotide release profiles following i.m. and s.c. administration of Autogel were similar. A Phase I study ([redacted]) was conducted to explore whether there was a preferred site for lanreotide Autogel administration. In this study healthy volunteers were given a deep subcutaneous injection of either 60, 90 or 120mg lanreotide Autogel over the deltoid, in the abdomen or in the buttock. Incidence of induration was less frequent when lanreotide Autogel was injected in the buttock and it was concluded that the buttock is the preferred site for deep subcutaneous injection.

A deep s.c. administration into the upper right quadrant of the buttock was used for Autogel efficacy studies to optimise patient acceptability and ease of administration.

IV.10.2 IV.2 In vitro dissolution studies

Development of an *in vitro* dissolution test presented a considerable challenge during development of the product, because lanreotide Autogel is a supersaturated solution and the conventional procedure of placing the product directly into the dissolution apparatus could not be used. Reports documenting the development of the method are presented in Module 3 of this application. A study to try to identify an *in vitro/ in vivo* correlation concluded that no correlation could be established.

IV.10.3 IV.3 Radiommunoassay methods

During the clinical development of lanreotide, four separate radiommunoassays (RIA) have been developed and used to determine lanreotide levels in human serum samples. All RIAs have employed the same principle, i.e., anti lanreotide antibodies raised in rabbits and are based on the competition between 125I-labelled and unlabelled lanreotide for binding sites on antibodies.

Validations of the RIA methods have been presented and can be summarised as follows: the detection limits range from 0.03ug/1 to0.08ug/1; the mean inter-assay variabilities range from 5.6 – 20%; the mean intra-assay variabilities range from 4.1 – 13.6%. In addition, a blind comparative study was carried out aiming to crossvalidate two of the RIA methods; this study demonstrated that the two methods were well correlated.

V. OVERVIEW OF CLINICAL PHARMACOLOGY

IV.10.4 V.1 Pharmacokinetics

The pharmacokinetics of lanreotide has been determined in numerous healthy volunteer studies following single s.c., i.v. and continuous s.c. dosing of the immediate release formulation. A number of studies are presented in the dossier reflecting a general pharmacokinetic profile of rapid absorption, a short mean residence time and limited extravascular distribution and rapid elimination.

IV.10.5 V.2 Immediate release lanreotide

One of the main studies using the immediate release formulation was [redacted]. This was a crossover study in which 12 subjects received doses of 7, 21 and 42 ug/kg/ s.c and 7 ug/kg/ i.v. The i.v. data demonstrated the lanreotide has a short half life of 1.44 hours, a short mean residence time of 0.59 hours and a relatively high plasma clearance of 0.30 1/kg/hr. These parameters indicate that lanreotide is rapidly eliminated from the body and accord with the low distribution volume (Vdβ) of 0.6 1/kg. The absolute bioavailability, obtained from comparison with a single s.c. dose of 7 ug/kg was very variable between subjects (55 to 126%) with a mean value of 82.8%. The pharmacokinetic data obtained following the single s.c. doses are provided in the Table 1. Absorption was rapid and tmax increased with increasing dose. Also, the data suggested that the value for tmax t1/2 and mean residence time (MRT) were dose dependent and that similarly, the AUC normalised for dose, increased with increasing doses. However, it is noted that only at the two higher s.c. doses were the plasma levels of lanreotide high enough to be modelling. At 7 ug/kg (i.v. and s.c.) the terminal t1/2 seems inflated as distribution is not complete. This is indicated by a statistically significant association between t1/2 calculated and follow up time. Because of this, the apparent dose-dependency of elimination t1/2,. MRT and AUC/D must be considered as a result of study design. Overall the data reflect a general pharmacokinetic profile of rapid absorption with rapid elimination from plasma and linearity with dose.

Redacted according to Section 40, FOI Act

TABLE 1: PHARMACOKINETIC PARAMETERS FOLLOWING SINGLE S.C.DOSES (N =12). SOURCE: STUDY [redacted] ([redacted]).

Redacted according to Section 40, FOI Act

	7ug/kg	21ug/kg	42ug/kg
T1/2 (h)	1.91	2.23	2.32
Cmax (ugIi)	12.32	30.55	58.21
Tmax (h)	0.38	0.50	0.85
AUC0 (ughIi)	19.21	63.96	146.86
AUC 0-t (ughIi)	18.83	63.14	144.45
MRT (h)	1.76	2.22	2.49
AUC/D (kghIi)	2.74	3.05	3.50
Cmax/D (kgIi)	1.76	1.45	1.39

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Study [redacted] investigated repeated s.c. administration of lanreotide immediate release formulation (10 injections of 7, 21, or 42 ug/kg given at 8 hour intervals). Results demonstrated linear pharmacokinetic behaviour between the 7 and the 21 ug/kg doses and low accumulation (mean ± SD values of the last-dose/first dose accumulation ration (Rac(AUC)) ranged from 1.05 ± 0.22 to 1.21 ± 0.23).

Two studies examined the excretion of lanreotide. When lanreotide IR was given as a single dose of 3 mg, less than 1% of the administered dose was recovered in urine and renal clearance was <1% of total plasma clearance ([redacted]). When lanreotide was given by s.c. infusion, the fraction of lanreotide excreted in the urine at steady state was 1% to 5% for a dose of 0.75mg/day. Data for faecal excretion were collected in this second study ([redacted]); less than 0.5% of the administered dose was recovered over a 24 hour period at a steady state. Therefore, urinary and faecal excretion represents only a small fraction of the total dose administered. This suggests that lanreotide is probably metabolised extensively in the gastrointestinal tract after biliary excretion. This is consistent with studies conducted in the rat, where biliary excretion accounts for 80% of the total lanreotide excreted.

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IV.10.6 V.3 Prolonged release microparticle formulation

A single pharmacokinetic study has been provided in this dossier to demonstrate the release profile of the microparticle formulation. The study ([redacted]) showed that lanreotide Microparticles given as a single 30mg intramuscular injection to healthy volunteers provided a mean peak serum concentration of 8.50 ng/ml achieved between 0.042 and 0.083 days post-dosing, reflecting the burst effect seen with this formulation. The mean area under the curve was of 32.34 ng/ml.day and lanreotide serum concentrations were detected in most subjects thirty two days after administration. After intra-muscular administration, lanreotide serum levels remained above 1ng/ml for an average of 12.81 days.

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IV.10.7 V.4 Lanreotide Autogel

IV.10.7.1 V.4.1 Autogel pharmacokinetics studies in healthy volunteers

A series of pharmacokinetic studies in healthy volunteers have been conducted during the development of lanreotide Autogel (described in the biopharmaceutics section of this report) using subcutaneous and intramuscular administration routes. A single study to confirm the release profile of lanreotide Autogel using the deep subcutaneous administration route proposed for the marketed product has been conducted in healthy subjects ([redacted]). Of the 54 subjects enrolled in this study, 50 received an initial dose of lanreotide immediate release formulation, but only 38 received the subsequent dose of lanreotide Autogel. This was due to knowledge of adverse events, primarily gastrointestinal, experienced in the first group of volunteers treated with lanreotide Autogel. Despite the high withdrawal rate, results from this study are consistent with the earlier development studies; the lanreotide release profile approximates log-linear, lanreotide exposure increased with Autogel dose. Other pharmacokinetic parameters were consistent between dose groups (see Table 2).

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TABLE 2: PHARMACOKINETIC PARAMETERS FOLLOWING DEEP SUBCUTANEOUS ADMINISTRATION OF LANREOTIDE AUTOGEL 60, 90 AND 120MG TO HEALTHY VOLUNTEERS. (SOURCE: INTERIM REPORT STUDY [redacted]).

Redacted according to Section 40, FOI Act

Parameter	60 mg			90 mg			120 mg		
	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%
Cmax (ng.ml1)	4.246	1.934	45.55	8.391	4.915	58.57	6.785	3.641	53.66
AUCt(ng.ml1h)	1634.61	435.19	26.62	2453.78	816.66	33.28	2984.81	1024.70	34.33

AUC ??(ng.ml1h)	1904.98	564.09	29.61	2984.35	1214.04	40.68	3552.26	947.33	26.67
T1/2(h)	664	455	68.52	860	431	50.12	816	334	40.93
Tmax(h)*	8 (4 to 336)	//	//	12 (4 to 336)	//	//	7 (2 to 48)	//	//
Tlag (h)	<1.0	0.0	//	<1.0	0.0	//	<1.0	0.0	//
MRT (h)	940.62	462.83	49.20	1009.87	568.17	56.26	1102.13	469.61	42.61
MAT (h)	939.78	463.00	49.27	1009.11	568.28	56.31	1101.29	469.49	42.63
F (%)	83.25	34.56	41.51	78.14	25.87	33.11	80.87	24.18	29.90

* = median and range in parenthesis

Dose proportionally by regression analysis was not observed for Cmx, due to the high interindividual variability in this parameter.

IV.10.7.2 V.4.2 Autogel pharmacokinetics studies in patients

In pivotal clinical efficacy and safety study [redacted], serum levels of lanreotide were taken immediately prior to dosing with lanreotide Autogel. It was therefore possible to compare trough serum lanreotide concentration after one, two and three deep s.c. doses of lanreotide Autogel with that achieved after at least 5 i.m. doses of lanreotide PR 30mg. Lanreotide serum level was described as one of the secondary endpoints of the study. Redacted according to Section 40, FOI Act

After the initial dose of lanreotide Autogel in this study, trough lanreotide levels were substantially lower than they had been at steady state on lanreotide PR 30mg. This was true for the per protocol population as a whole, as well as for each lanreotide Autogel dose group, although data were not available for all patients. By the time patients had reached the end of the study period, the trough serum lanreotide levels achieved on Autogel were similar to those achieved at steady rate on lanreotide PR 30mg.

For the 60mg lanreotide Autogel dose group, at trough levels after the third injection, median serum lanreotide was 1.63 ng/ml (range 0.81 – 3.17 ng/ml). For the 90 mg dose group median serum lanreotide level was 2.18 ng/ml (range 1.14 – 7.22 ng/ml) and for the 120mg Autogel dose group median serum lanreotide level at trough after the third injection was 2.48 ng/ml (range 1.51 – 4.63 ng/ml).

In all three dose groups trough levels of lanreotide continued to rise from the first dose to the third dose, and it is not possible to conclude from this study that patients had reached steady state.

Study [redacted] was a long term follow up to [redacted]. Patients who completed [redacted] continued to take lanreotide Autogel for a period of one year. The study allowed the dose of Autogel to be titrated up or down according to the GH level achieved. When the Gh level remained between 1 ng/ml and 2.5 ng/ml, patients stayed on the same dose of lanreotide Autogel, allowing for the determination of time taken to steady state and trough lanreotide serum levels at steady state. Redacted according to Section 40, FOI Act

A pharmacokinetic analysis has been completed which allows for some useful conclusions to be drawn about the pharmacokinetics of lanreotide Autogel in this patient population. These results are described in full in report 01/PKR/50.

Because of the nature of the clinical protocol, where patients were permitted to titrate the dose of lanreotide Autogel according to the control of their acromegaly, the numbers of patients who stayed on the same dose was inevitably small. Trough serum lanreotide levels were available after 15 consecutive monthly injections of the same lanreotide Autogel dose for the following numbers of patients:

60 mg lanreotide Autogel: n = 31
90mg lanreotide Autogel: n = 10
120 mg lanreotide Autogel: n – 19

Despite these relatively small numbers, it is possible to draw meaningful conclusions from the data. In all the lanreotide Autogel dose groups (60, 90 and 120mg) the mean trough serum levels of lanreotide at steady state were not statistically significantly different from the mean trough serum lanreotide levels seen on lanreotide PR 30 mg at equivalent dose. These results are compared with those obtained on lanreotide PR30 mg in Table 2.5.3.1-3.

TABLE 3: COMPARATIVE MEAN TROUGH SERUM LANREOTIDE LEVELS (NG/ML) AT STEADY STATE IN ACROMEGALIC PATIENTS FOLLOWING 5 I.M. INJECTIONS OF LANREOTIDE MICROPARTICLES 30 MG AT A DOSE FREQUENCY OF 14, 10 AND 7 DAYS AND FOLLOWING REPEATED DEEP SUBCUTANEOUS INJECTIONS OF LANREOTIDE AUTOGEL AT THE SAME DOSES OF 60, 90 AND 120 MG RESPECTIVELY, ONCE MONTHLY.

	Lanreotide Autogel Dose		
	60mg n = 31	**90mg n = 10**	**120mg n=19**
Cminss PR30	1.94 (0.72)	2.95 (1.60)	3.06 (1.15)
Cminss Autogel	2.07 (0.62)	3.08 (0.52)	3.32 (1.30)

Cminss PR 30: Trough serum lanreotide level at steady state after 5 doses of lanreotide PR 30 mg.

Cminss Autogel: Trough serum lanreotide level after repeated doses of lanreotide Autogel.

Note: All patients on 60mg lanreotide Autogel are compared with lanreotide PR 30mg once every 14 days; all patients on lanreotide Autogel 90mg are compared with lanreotide PR 30mg once every 7 days.

Steady state was achieved after 4 injections on lanreotide Autogel in most patients, although some patients did not achieve steady state until 5 to 7 injections. There was no evidence of accumulation of lanreotide after multiple injections of Autogel in any dose group.

These findings confirm the suitability of lanreotide Autogel for once monthly dosing by the deep subcutaneous route. They also provide good pharmacokinetic evidence for the choice of doses and the dosing interval chosen for the pivotal efficacy/ safety studies.

IV.10.7.3 V.4.3 Intrinsic pharmacokinetic factors

Studies of intrinsic factor effects on lanreotide pharmacokinetics have shown that subjects with sever renal impairment show an approximately 2-fold decrease in total serum clearance of lanreotide, with a consequent increase in half-life and AUC. In hepatic impairment an increase in volume of distribution, mean residence time, AUC and half-life were observed. Clearance was reduced by 30% in these patients in one study and unaltered compared to healthy subjects in a second, suggesting that clearance of lanreotide does not depend on hepatic function alone. Elderly subjects showed an increase in half-life and mean residence time compared with healthy young subjects. Although there are some differences observed in the pharmacokinetics of lanreotide in these populations, because lanreotide has a wide therapeutic window and dosage is titrated against reduction in GH and IGF-1, it is not considered necessary to alter the dose recommendations for lanreotide in Autogel.

IV.10.7.4 V.4.4 Extrinsic pharmacokinetic factors

Studies examining potential for interference between lanreotide and other drugs revealed that lanreotide decreased the bioavailability of oral cyclosporin by approximately 20%. An appropriate warning is provided in the SmPC. The same study demonstrated a lack of any interaction with vitamin K.

IV.10.7.5 V.4.5 Plasma protein binding

Lanreotide has a low affinity for binding to serum proteins (mean percentage bound 78%) and shows no saturation within the therapeutic range studied (5 to 370nM). Binding to human serum albumin (HAS) and alpha acid glycoprotein (AAG) represented 36% and 25% of the total binding. In view of the low affinity for binding the risk of drug interactions associated with binding to plasma or serum is low. The relevance of protein binding to therapeutic performance is also unlikely to be significant.

IV.10.7.6 V.4.6 Pharmacodynamics

Pharmacodynamic studies carried out during the development of this agent included the use of the immediate release form, given intravenously and subcutaneously, and of the prolonged release microparticle form given intramuscularly. The main dynamic variables measured were circulating GH concentrations and IGF-1 as surrogate markers for acromegaly status. The immediate release formulation was investigated in several placebo-controlled dose-ranging studies at doses between 125ug daily and 80ug/kg (approx 5.6mg) daily.

IV.10.7.7 V.4.7 Pharmacodynamic action related to the therapeutic effect

IV.10.7.7.1 V.4.7.1 Subcutaneous (s.c.) dose studies in healthy volunteers – effect on GH levels

Reports are provided of five placebo-controlled, cross over studies in which healthy male volunteers received single s.c. doses ranging from 125 ug to 80 ug/kg (the latter equivalent to 5.6mg in a 70kg man) (study report numbers [redacted]). In two of these studies, the daily doses were split to be either two doses separated by 12 hours, or three doses each separated by seven hours

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([redacted]). Each study involved between six to twelve subjects and the area under the GH curve was the major parameter evaluated. Redacted according to Section 40, FOI Act

The results demonstrate that a wide range of lanreotide doses reduces GH levels. For example, a significant effect was found on nocturnal GH secretion following a dose of 500 ug, with the plasma Growth Hormone AUC $_{0\text{-}6hr}$ being reduced by a Hormone-Releasing Hormone (GH-RH) stimulation, a reduction in the serum GH AUC value of 37% was found after a dose of 750 ug (given as three doses of 250ug) ([redacted]). Doses of 5 and 80 ug/kg were shown to completely suppress the increase in serum GH following stimulation by infusion of amino acid ([redacted]).

IV.10.7.7.2 V.4.7.2 Continuous s.c. infusion (up to 24hr) studies in volunteers – effect on GH levels

In two placebo-controlled s.c. infusion studies ([redacted]), lanreotide's ability to maintain consistently reduced GH levels during continuous therapy was demonstrated. When administered as a continuous s.c. infusion of 2000ug over 12 hours, lanreotide significantly reduced nocturnal plasma GH secretion ($AUC_{0\text{-}12hr}$ reduced by a mean of 72% compared with placebo; p=0.02). Stimulation of GH secretion with GH-RH was also significantly reduced by lanreotide, given at the same dosage (mean decrease of $AUC_{0\text{-}12hr}$ of 67%; p=0.001) ([redacted]).

In the second s.c. infusion study doses of 1000, 2000 and 3000 ug were administered over 24 hours ([redacted]). The results demonstrated a dose related and significant reduction in mean plasma $AUC_{0\text{-}24hr}$ of 65%, 73% and 77% for each dosage group respectively, when compared to a placebo, although the actual GH levels (ug/24h/1), were not significantly different between the treatment groups. The number of volunteers studied here was probably insufficient to identify a clear cut dose response, if present, in a four way cross over design. However, these initial studies indicate that the most appropriate starting dose in pharmacokinetic studies in patients would be 1000ug daily of the immediate release formulation.

This in fact was demonstrated in the studies of the immediate release formulation in acromegaly patients ([redacted]) where continuous s.c. infusion was shown to be effective in reducing GH levels, resulting in alleviation of symptoms.

IV.10.7.8 V.4.8 Studies in patients with acromegaly

In a placebo-controlled, cross over study in six patients ([redacted]), the effect of single c.s. doses (1500ug: given either as 750ug every 12 hours or 500ug every 8 hours) was compared with a continuous s.c. infusion of the 1500ug given over 24 hours. Mean baseline plasma GH levels ranged from 32 to 47ug/1 for the four treatments. With the single doses, levels fell significantly to values less than 10ug when measured at 4 hours post the first injection, but thereafter values rose by about 20ug/1 within 8 hours of dosing. A similar pattern was seen following the second and third injection. Only during the continuous therapy did the GH levels remain significantly reduced during the treatment period, with values ranging from 2 to 3.5 ug/1 ($p \leq 0.01$). In the second part of this study a dose related reduction in GH levels was demonstrated with continuous s.c. infusion doses of 500, 1000 and 1500ug, each administered over 24 hours. The reductions in plasma GH values were constant over the infusion period. This is confirmed by the results of the other study in acromegalic patients

([redacted]) where lanreotide was administered in doses up to 2000ug/day by continuous s.c. infusion. Redacted according to Section 40, FOI Act

In a study involving sixteen acromegalic patients, daily doses of 1000, 1500 or 2000ug were administered by continuous s.c. infusion ([redacted]). In a separate study ([redacted]) in five subjects who received seven days continuous s.c. infusion of wither placebo or lanreotide 2000ug/day, the plasma IGF-1 level decreased significantly (p,0.05) by 30% from a mean day 1 value of 250.6ng/ml to a mean day 7 value of 177.8ng/ml in the lanreotide-treated group.

Only continuous infusion of lanreotide at a dosage of at least 1000ug daily maintained the reduction in GH and IGF-1 and consequently this dosage was selected for the subsequent study in 16 patients. The criterion for entry in this subsequent study was active acromegaly in spite of previous surgery or radiotherapy. This led to the selection of a very heterogeneous patient population with wide variation in baseline GH, IGF-1 levels and symptoms. This study, although well-conducted, clearly demonstrated the importance of including a reasonably homogenous group of patients in a study, especially since this population who failed with conventional treatment was more prone to having different baseline variables, both symptomatic and biochemical. In addition it needs to be pointed out that the reductions in GH and IGF-1 were not of the same order of magnitude as those observed with healthy volunteers. This is undoubtedly a reflection of the different baseline levels and together with the small numbers and high variability makes data interpretation difficult.

Nonetheless, from the studies presented it is clear that lanreotide given s.c. inhibits the secretion of both IGF-1 and GH. Furthermore, continuous infusion therapy, at doses above 1000ug/24 hours, has been demonstrated to be necessary in order to provide a constant significant reduction in GH levels. A dose response was demonstrated in the two studies, which evaluated continuous s.c. infusion over a 24 hour period for doses ranging from 1000 to 3000ug/24 hours ([redacted]) and 500 to 1500ug/24 hours ([redacted]).

In addition to the biochemical indices, the effect of lanreotide on symptoms (such as headache and sweating) appears to be quite dramatic indicating the effectiveness of treatment.

These studies in acromegaly patients with the immediate release formulation clearly demonstrated the requirement for a sustained or prolonged release formulation of lanreotide.

Pharmacodynamic studies of a single dose, sustained release formulation of lanreotide PR (30mg), were carried out in healthy subjects ([redacted]) and in acromegaly patients ([redacted]). In the two small studies in healthy volunteers, the changes seen in IGF-1, set against lanreotide plasma levels, demonstrated that these were dependent upon baseline IGF-1 levels. Although the reduction in IGF-1 levels are statistically significant at day 14 after treatment, it appears from the data that the reduction in IGF-1 may still be clinically relevant up to 18 days but after this the levels return to near baseline values. These two studies assessing the effect of a single i.m. injection of sustained release lanreotide were encouraging in the consistency of the results, although dependent on baseline IGF-1 and were sufficient to encourage the study of this formulation in patients.

The pharmacodynamic studies in acromegaly patients were both similar in design, patient population and patient numbers. A single dose of 30mg lanreotide was administered i.m. and the data emerging were consistent between the two studies ([redacted]). It was apparent that the sustained release formulation produced results confirming a pharmacological effect up to 14 days similar to that in healthy volunteers.

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Three Population pharmacokinetic and pharmacodynamic studies to investigate the relationship between lanreotide serum levels and GH plasma levels at steady state have been performed in acromegalic patients already shown to respond to lanreotide. In the first study ([redacted]) the study population consisted of 63 responder patients from 5 studies in which lanreotide was administered at a range of doses, routes and durations, either as the microparticle formulation (lanreotide PR 30mg) or as an immediate release form of the drug. Only the acromegalic patients that responded to the treatment were included in the pharmacokinetic-pharmacodynamic analysis (decrease of at least 50% in GH basal levels or a normalisation of GH levels to $\leq$2.5ng/ml).

Lanreotide serum levels were plotted against GH levels and two models were fitted to the data (Inhibitory Emax Model and Inhibitory Sigmoid Emax Model). The best fit model was used to estimate EC_{50} and $C_{2.5}$ values (i.e., the concentrations of lanreotide required to reduce basal GH levels by 50% and to reduce GH levels to 2.5ng/ml, respectively). Data was studies on a patient by patient basis (individual) and on a per study basis (global).

Fifty four patients were available for individual analysis. EC_{50} for lanreotide was 0.5ng/ml. Lanreotide levels necessary to achieve mean GH levels below 2.5ng/ml were estimated as follows: (Table 2.5.3.2-1).

TABLE 4: FREQUENCY AND CUMULATIVE % OF PATIENTS WITH GH LEVELS LESS THAN 2.5 NG/ML CATEGORISED BY SERUM LANREOTIDE LEVEL.

Lanreotide levels (ng/ ml)	Number of patients	Number of patients % (frequency)	Cumulative number of patients	Cumulative %
0-0.5	2	4%	2	4%
0.5-1	9	17%	11	20%
1-1.5	14	26%	25	46%
1.5-2	7	13%	32	59%
2-2.5	4	7%	36	67%
2.5-3	2	4%	38	70%
3-3.5	6	11%	44	81%
3.5-4	1	2%	45	83%
4-5	4	7%	49	91%
5-6	0	0%	49	91%
6-7	2	4%	51	94%
7-10	1	2%	52	96%
More	2	4%	54	100%

Thus lanreotide concentrations up to 2 ng/ml were estimated to be necessary to achieve mean GH levels below 2.5 ng/ml in 60% of patients. Lanreotide levels up to 3.5 ng/ml were estimated to be necessary to achieve means GH levels below 2.5 ng/ml in 81% of patients.

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Two further population pharmacodynamic/ pharmacokinetic analyses have been conducted using data from pivotal Phase III studies, one in patients treated with lanreotide 30mg Microparticles ([redacted]) and a second analysis in patients treated with lanreotide Autogel ([redacted]). The aim of these analyses was to study the relationship between lanreotide and GH serum levels under steady state conditions. Population pharmacodynamic parameters Emax (the maximum reduction of GH from basal values) and EC50 (the inhibitory lanreotide serum level that decreases GH by 50% of Emax) were determined and are presented in Table 2.5.3.2-2.

These studies also broadly confirm the results of study [redacted], where the concentration of lanreotide required to decrease the GH levels to 2.5 ng/ml (C_{25}) was calculated as 3.5ng/ml. As in [redacted], the C_{25} analysis suffered from inherent difficulties resulting from design of the Phase III protocols, resulting in a smaller patient population that could be included in the analysis and a high degree of variability in results. The C_{25} values quoted are 1.895 ± 4.286ng/ml (mean ± SD) for [redacted] and 1.127ng/ml (median) for [redacted].

Table 5: Population pharmacodynamic parameters calculated from lanreotide microparticle and lanreotide Autogel Phase III studies

PK/PD analysis	Parameter	Value	Relative Standard error	Inter-individual variability
[redacted] (data from lanreotide microparticle Phase III studies [redacted])	EMAX	0.843 ng/ml	±5.04%	17.94%
	EC50	0.375 ng/ml	±25.87%	93.91%
[redacted] (data from Phase III lanreotide Autogel studies [redacted])	EMAX	0.821 ng/ml	±7.53%	-
	EC50	0.206 ng/ml	±50.00%	200.75%

These population PK/PD analyses show lanreotide acts similarly to reduce GH levels, whether released from the microparticle or the Autogel formulation. Consequently the Phase III studies using the prolonged release microparticle formulation provide further support for the efficacy of lanreotide Autogel and efficacy data on three pivotal microparticle studies in acromegalics are presented in this application.

IV.10.7.9 V.4.9 Pharmacodynamic actions not related to the therapeutic effect

Somatostatin, as well as inhibiting the release of GH from the anterior pituitary, also can inhibit the release of thyrotrophin, corticotrophin and luteinsing hormone from the pituitary, glucagon and insulin from the pancreas, and appears to have a role in the regulation of duodenal and gastric secretions. Although the somatostatin analogues have a greater specificity of action than the native molecule, they nevertheless inhibit the secretion of

insulin and glucagon, and hence could cause disturbances to glucose homeostasis. This potential has been investigated.

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In a placebo-controlled, crossover study in eight subjects, doses of 1000, 2000 and 3000ug were given by continuous s.c. infusion over 24 hours ([redacted]). Lanreotide caused a change in the post prandial (breakfast) response of the principle plasma indices of glucose regulations namely, glucose, insulin, C- peptide and glucagon. The results showed essentially that there was a delay in the response time of insulin and C-peptide to the food stimulus and that their circulating levels were lower than control values, while glucose levels increased above control values. These profiles resulted in an increased AUC for glucose of about 15% for the top two doses and a significant decrease in AUC levels of more than 50% for insulin and C-peptide at all dose levels. Glucagon levels were lowered, especially at the top dose, but the difference was not significant when compared with placebo.

Similar results were also found in the single dose studies involving orally induced hyperglycaemia ([redacted]) and the concomitant administration of amino acid infusions, used to stimulate GH release ([redacted]). In a study in which lanreotide was given by a continuous s.c. infusion at a dose of 2000ug/day for 7 days ([redacted]), an effect on glucose regulation was found on day one. However, after six days administration, the effects had disappeared except for a slight delay in the occurrence of the insulin peak by about 30 minutes. This situation is supported by the results from the clinical trials which show that fluctuations in blood sugar levels in patients were small. There are, however, only limited data on the effects of lanreotide in patients with non-insulin dependent diabetes mellitus and a suitable precaution regarding the use of the product in diabetic patients is included in the SmPC.

Three studies have been conducted to examine the effect of lanreotide on renal and splanchnic blood flow ([redacted]). These studies showed that lanreotide decreases superior mesenteric artery and portal venous blood flow but has no effect on renal blood flow.

In Study [redacted] the effect of lanreotide on the secretion of digestive hormones was investigated. Following s.c. infusion of a dose of 2000ug over 12 hours, there was a significant inhibition of the secretion of motilin and pancreatic polypeptide (by about 65%) compared to placebo. Reductions in plasma levels of pancreatic polypeptide, motilin and gastric inhibitory peptide also occurred during the seven days of continuous s.c. infusion of 2000ug/day in Study [redacted]. Such results accord with the pharmacological profile of lanreotide and may in addition, play a role in the gastrointestinal adverse events seen during the clinical trials.

Other dynamic studies conducted with lanreotide included the effect on jejunal secretion of water and electrolytes following i.v. administration ([redacted]), the secretion of TSH ([redacted]) and of glucagon ([redacted]) following s.c. administration; all in healthy volunteers. The studies confirmed consistent effects of lanreotide in reducing PGE-1-stimulated water and electrolyte secretion from the jejunum and the TSH response to TRH. Basal TSH was not altered. The effects on stimulated TSH did no, however, result in any biochemical evidence of hypothyroidism. The potential side effects on thyroid hormone and insulin secretion do not appear to be clinically significant, although

the reduction in cholecystoknin secretion ([redacted]) may be relevant to potential effects on gall bladder contraction and gall stone formation. Redacted according to Section 40, FOI Act

IV.10.7.10 V.4.10 Immunogenicity

Potential for formation of lanreotide antibodies has been examined during the conduct of efficacy studies using both the microparticle formulation and lanreotide Autogel. Results from Autogel studies ([redacted] are similar to those found in earlier microparticle studies ([redacted] [N= 83] and [redacted] [N=17]).

All 130 of the patients in study [redacted] had at least one measurement of anti-lanreotide antibodies after treatment with lanreotide Autogel. However, only 4 patients had one or more samples with non-specific binding (NSB) values of >30%.

While on treatment with lanreotide Autogel. A further 12 patients had NSB values of 10-30% on at least one occasion while receiving lanreotide Autogel, although in 11 of them NSB values >10% were measured while they were receiving the previous microparticle formulation as well. A probable specific antibody response to lanreotide Autogel was therefore detected in only 4 of 130 patients. The safety profile of patients with non-specific binding values <10%, between 10 and 30% and >30% were similar and there was no evidence that any of the serious adverse events that were reported were due to hypersensitivity reactions. Comparison of the efficacy data from patients with non-specific binding >110% compared to the total ITT population shows that efficacy response in terms of control of GH or IGF-1 levels is unaltered.

VI. OVERVIEW OF EFFICACY

IV.10.8 VI.1 Introduction

The main lanreotide Autogel efficacy study presented in this submission is [redacted], in which patients were switched from lanreotide Microparticles to lanreotide Autogel at fixed doses. These patients then went on to a second study ([redacted]) in which they receive titrated doses of lanreotide Autogel for 12 months. In view of this development history, this application presents data on three pivotal studies in acromegaly ([redacted]) with the widely marketed Microparticle formulation; the 'switch' study ([redacted]) demonstrating the long term efficacy and safety of this new product.

All of the studies conducted and included in this application were open label due to the small numbers of patients that were available for recruitment in this orphan indication. Each involved the treatment of a significant number of patients over a long duration, had validated databases and were conducted according to current Good Clinical Practice (GCP) guidelines. Additional supporting data for the efficacy claims of this application have been supplied in one additional lanreotide Autogel study and seven lanreotide Microparticle studies.

IV.10.9 VI.2 Study endpoints

The important efficacy endpoints for these studies were Gh (Growth Hormone) and IGF-1 (Insulin like Growth Factor – 1) levels. Reduction in GH levels is known to reverse the acute

disease complications and decrease mortality associated with acromegaly. As the effects of GH are mediated predominantly through IGF-1, the latter has also become an increasingly important measure in the treatment of acromegaly. In the studies presented in this application it is difficult to compare efficacy results across the studies. Over the duration of the development program for lanreotide the criteria for disease control have become more stringent. In the early 1980s the biochemical goal was GH<10ng/ml, later studies used a criterion of GH<5ng/ml and in the 1990s this was reduced to GH levels<2.5ng/ml.

The uncontrolled studies in this application have used baseline controls. There are three primary reasons for this:- (1) treatments that lower GH concentrations decrease morbidity and mortality, and therefore many consider placebo trials unethical; (2) since acromegaly is a rare disease, there are insufficient numbers of patients to conduct large, Phase III, controlled studies; (3) the treatment modalities are sufficiently different to make parallel group trials logistically difficult.

The non- comparative, baseline-control design, used in many of the studies, is valid because acromegaly is a stable or progressive disease. Analysis of the efficacy variables, GH and IGF-1 level, were separated into primary and secondary parameters.

IV.10.9.1 VI.2.1 Primary Parameters

2 Proportion of patients with controlled GH levels (GH $\leq$ 2.5ng/ml or GH $\leq$ 5ng/ml).

3 Proportion of patients with controlled IGF-1 levels.

IV.10.9.2 VI.2.2 Secondary Parameters

2 Proportion of patients with controlled GH (GH $\leq$ 2.5ng/ml or GH $\leq$ 5ng/ml) and controlled IGF-1 levels.

3 Descriptive statistics and changes in GH concentrations over time

4 Descriptive statistics and changes in IGF – 1 concentration over time

5 Changes in the intensity of acromegaly symptoms over time

IV.10.10 VI.3 Primary Efficacy Studies

IV.10.10.1 VI.3.1 Pivotal lanreotide Autogel studies

IV.10.10.1.1 VI.3.1.1 Study [redacted]

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Study design

All patients had been treated with lanreotide PR 30 mg for at least three months prior to entry into the study. After entry into the study, treatment with lanreotide 30mg PR was continued at the same dose interval during a run-in period, when patients received five injections of lanreotide Microparticles. At the end of the run-in period, patients then received three deep s.c. injections of lanreotide Autogel every 28 days, for a total duration of 12 weeks (the day

of the first lanreotide Autogel injections was also the final day of the last dosing interval of the run in period).

Each patient was switched to 60, 90 or 120 mg of lanreotide Autogel dependent on whether the dosing interval of lanreotide PR 30mg at the end of the run in period was between 12 and 16 days, 8 and 11 days or 5 and 7 days, respectively. The effect of this was to ensure that patients continued to receive the same monthly total lanreotide dose.

The primary objective of the study was to demonstrate that lanreotide Autogel formulation is no less effective than lanreotide Microparticles on mean GH level. Lanreotide Autogel was considered as non-inferior to lanreotide Microparticles in the upper limit of the 95% confidence interval did not exceed 1.25 (analysis of variance testing).

The secondary objectives were:

2 To demonstrate that lanreotide Autogel is no less effective than lanreotide 30mg PR on IGF-1 level.

3 To document the following parameters after one and three repeated monthly administrations of lanreotide Autogel at fixed doses: normalisation of GH ($\leq$ 5ng/ml and $\leq$ 2.5 ng/ml) and IGF-1 levels, GH and IGF-1 serum levels, evolution of acromegaly symptoms, lanreotide serum levels, anti lanreotide antibodies and safety (local and systematic tolerance, standard haematology and biochemistry, ultrasound of gall- bladder and anti diabetic treatment).

4 To compare the previous parameters after three repeated administrations of lanreotide Autogel to those observed just before the 5th injection of lanreotide PR 30mg in the run in period.

Study population

144 patients (48% male: 52% female) were recruited on to the study and received at least one dose of lanreotide Microparticles or lanreotide Autogel (safety populations). 132 of these patients had data for one or more key efficacy variables (ITT population) and 107 of these patients were not major protocol violators and were included in the PP population.

The demographic (age, weight height and race) and baseline characteristics were similar for the PP and safety population. Median time since diagnosis of acromegaly was eight years, 77% of the patients had had previous pituitary surgery and 44% had had previous radiotherapy.

The most common medical history (PP population) was unspecified essential hypertension reported by 54 (38%) patients. Sixty nine (48%) patients reported a history of gall bladder disorder. Forty (28%) patients reported a history of diabetes. 49% of the patients had received lanreotide PR 30mg before the study at a dosing interval of 14 days compared to 29% and 18% of the patients who had been dosed at a 10 day interval and 7 day interval respectively.

Efficacy evaluation

In the PP population, the upper boundary 95% confidence intervals of the ration of the geometric means of mean GH and IGF-1 levels at the end of the fourth interval of lanreotide Microparticles and at the end of the third interval at lanreotide Autogel were 1.041 and 1.034 respectively. These confidence intervals were lower than the 1.25 limit set for non-inferiority, demonstrating that lanreotide Autogel is no less effective than lanreotide Microparticles. The results of the non- inferiority analysis of mean GH and IGF-1 in the ITT population data were similar (upper 95% CI: 1.078 and 1.022 respectively).

Median GH and median IGF-1 were higher at the end of the first interval of lanreotide Autogel than at the end of the fourth interval of lanreotide Microparticles or at the end of the third interval of lanreotide Autogel. This was to be expected and resulted from a transient decrease in lanreotide serum levels when the switch from Microparticles to lanreotide Autogel occurred. The transient decrease is cause by the smaller carry- over effect from the shorter lasting Microparticle formulation, which becomes apparent during the two weeks before the second Autogel administration. Median GH and median IGF-1 were lower at the end of the third interval of lanreotide Autogel than at the end of the fourth interval of lanreotide Microparticles.

Median GH and median IGF-1 levels were highest in the 120mg lanreotide Autogel group and lowers in the 60mg lanreotide Autogel group at the end of the fourth interval of lanreotide Microparticles and at the end of the third interval of lanreotide Autogel. This probably reflects the fact that the patients who are most resistant to treatment will receive the highest dose of lanreotide, and because steady state has not yet been achieved by the third month of treatment with Autogel. These results are shown in Table 5.

Table 5: Median trough GH and IGF-1 levels (ng/ml) after treatment with lanreotide Microparticles compared with median GH and IGF-1 levels after treatment with lanreotide Autogel every 28 days for 3 months

Lanreotide Autogel dose	**End 4th interval lanreotide PR 30mg**	**End 3rd interval lanreotide Autogel**
	GH (ng/ml)	
All doses (n=107)	2.53	2.21
60mg (n=52)	2.37	1.88
90mg (n=34)	2.14	2.31
120mg (n=21)	3.06	3.59
	IGF-1 (ng/ml)	
All doses (n=107)	296	285
60mg (n=52)	245	245
90mg (n=34)	300	276
120mg (n=21)	408	359

The percentage of patients with mean GH < 2.5 ng/ml and both mean GH < 2.5 ng/ml and normalised IGF-1 were statistically significantly higher at the end of the third interval of

lanreotide Autogel (56% [60/107] and 39% [42/107] respectively) than at the end of the fourth interval of lanreotide Microparticles (48% [51/107 and 33% [33/107]).

The most common acromegaly symptom suffered by patients during treatment with lanreotide PR 30 mg and lanreotide Autogel was joint pain (38% [41/107] and 38% [40/106] patients respectively). The least common acromegaly symptom suffered by patients during treatment with lanreotide Microparticles and lanreotide Autogel was night sweats (23% [25/107] and 21% [22/106 patients, respectively).

The total numbers and percentages of patients with each acromegalic symptom were similar at the end of the third interval of lanreotide Autogel and at the end of the fourth interval of lanreotide Microparticles. Most patients reported acromegalic symptoms that were mild or moderate in severity. The ITT population data were similar.

IV.10.10.1.2 VI.3.1.2 Study [redacted]

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Study design

Study [redacted] was designed as a follow-on study from study [redacted] recruiting patients who had completed treatment in that pivotal efficacy study. The primary objective was to demonstrate that after 12 repeated deep subcutaneous injections of lanreotide Autogel (every 28 days) at titrated doses (60, 90, or 120mg) the biochemical efficacy in terms of means GH levels is higher than that observed after three fixed dose injections in the switching Phase III study ([redacted]).

The design of this study recognised that the current treatment target in acromegaly is to reduce the mean GH to a low level below 2.5ng/ml. The protocol allowed the patient to increase the dose of lanreotide Autogel if their GH level was above 2.5ng/ml and to decrease the dose of lanreotide Autogel if their means GH was below 1ng/ml/ The study therefore allowed for the optimisation of the GH response to lanreotide and demonstrated what proportion of acromegalic patients require each of the three available doses. Lanreotide plasma levels were collected after 4, 8 and 12 months of treatment. Despite patients changing dose during the study some valuable pharmacokinetic conclusions could be drawn from a more complex analysis of the relationship between exposure to lanreotide and reduction in GH and/or IGF-1.

Study population

13 patients were recruited from the 131 patients who had completed the preceding study and had received at least one dose of lanreotide Autogel. Six patients were not included in the intent to treat population as they had no efficacy data at visit V4 or after (ITT: N=124). 88 patients fulfilled the criteria to be included in the PP population. Age ranged from 25 to 77 years, with a median of 53.3 years. There were a comparable number of males and females in the study (63 vs. 67) and the majority of patients were Caucasian (98%). Median time since diagnosis of acromegaly was 8.26 years in the ITT population. The most common medical history was essential hypertension in 38% of the safety population.

Efficacy evaluation

In the ITT population the mean GH level was reduced after 12 repeated administrations of lanreotide Autogel at titrated doses (visit V16) from the observed at the end of the previous study ([redacted]) in which patients received lanreotide Autogel at fixed doses for 3

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months (visit V4). Reduction in mean GH levels was also observed with each of the titrated doses of lanreotide Autogel. Repeated administration of lanreotide Autogel at titrated doses was also associated with a significant decrease in mean IGF-1 level from visits V4 to V16. The reductions in mean GH levels associated with lanreotide Autogel treatment at titrated doses were accompanied by increases in the proportion of patients who had GH levels $\leq$ 2.5 ng/ml, $\leq$ 5.0 ng/ml and normalised IGF-1 levels. At V4, 55% of patients had GH levels $\leq$ 2.5 ng/ml. This proportion increased to 68% at the end of treatment (V16). The proportion of patients with GH levels $\leq$ 5.0 ng/ml also increased from 81% at V4 to 93% at V16. The numbers of patients with normalised IGF-1 levels was similar at visit V4 (N=61 (49%)) and at visit V16 (N=62(50%)). The number of patients with high GH levels $\leq$ 2.5 ng/ml and normalised IGF-1 increased from 48 (39%) at V4 to 52 (43%) at visit V16.

Table 6: Summary of GH and IGF-1 levels (ng/ml) (ITT population).

All lanreotide Autogel doses		**End of 4th interval Visit R5 N=124**	**End of 3rd interval Visit V4 N=124**	**End of 15th interval Visit V16 N=123**
Formulation		Microparticles	Autogel	Autogel
GH				
	Mean ± SD Median Min, Max	2.82±2.0 2.52 0.5, 8.5	3.02±2.33 2.27 0.5, 10.5	2.38±2.0 1.96 0.5, 13.2
IGF-1	Mean ± SD Median Min, Max	322.2±168.2 292.5 73, 985	310.4±153.8 279.5 80, 918	287.5±137.1 271.0 56, 949

Symptoms of acromegaly were improved after 12 repeated administrations of lanreotide Autogel (visit V16), as compared with results obtained at the end of the previous study (visit V4). Improvements associated with treatment were observed in a substantial proportion of patients for night sweats (9%), headache (15%), asthenia (16%), swelling of extremities (17%) and joint pain (14%) Worsening was reported by only 4% (night sweats), 6%(headaches), 8% (asthenia), 9% (swelling of the extremities), and 11% (joint pain) of these patients.

Mean serum levels of lanreotide increased with increasing doses of lanreotide Autogel. Increasing serum levels were associated with reductions in serum GH and IGF-1 levels over the course of the treatment.

IV.10.10.2 VI.3.2 Key lanreotide Microparticle studies

IV.10.10.2.1 VI.3.2.1 Combined study [redacted]

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Study report [redacted] presents the combined data of two studies. 85 patients were enrolled in [redacted] and 75 continued on into [redacted] (minimum treatment duration of 52 weeks on the most effective dosing schedule). Patients had not received radiotherapy or undergone pituitary surgery within three months of inclusion. Those receiving somatostatin analogues underwent a two week wash out period prior to the first lanreotide injection. In [redacted] patients initially received lanreotide Microparticles once every 14 days. If GH and/or IGF-1 levels were normalised patients increased to one

injection every 10 days. In study [redacted] patients continued on their dosing schedule or were increased again to once every 7 days if control had not been obtained. At the end of the study 23 patients were in the 14-day regimen, 15 were in the 10 day regimen and 47 were inn the 7 day regimen. Lanreotide was shown to be effective in reducing GH and IGF-1 levels in acromegalic patients. The median GH concentration in the ITT population decreased from 5.12ng/ml at baseline to 1.98 ng/ml at the LVA. Increase frequency of dosing in patients who had failed to respond increased the overall proportion of patients who responded to lanreotide.

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IV.10.10.2.2 VI.3.2.2Combined study [redacted]

Study report [redacted] also presents the combined data of two US studies in 'De novo' patients who had not undergone pituitary surgery or received radiotherapy previously, or been treated with somatostatin analogues. Again patients initially received one injection of lanreotide Microparticles every 14 days but this could be increased to every 10 days or every 7 days (in study [redacted]) depending on the patient's response. Of the 24 patients enrolled 19 completed and were included in the ITT populations. None of these were in the 14- day regimen, three were in the 10- day regimen and 16 were in the 7 day regimen.

35.3% (6/17) patients met the average over-time GH cut off level of <2.5ng/ml, 10.5% (2/19) met the over-time IGF-1 normalisation criterion and 11.8% (2/17) met the average over time criteria for control of both GH and IGF-1. The median of the reduction in GH concentrations was 71.5% and the median of the reduction in IGF-1 concentrations was 54.0%. The median GH concentration in the ITT population decreased from 8.95 ng/ml at baseline to 3.56 ng/ml at the LVA.

Lanreotide was shown to be effective in reducing GH and IGF-1 levels in acromegalic patients who had not been previously treated with surgery, radiotherapy, or somatostatin analogues. Increasing the frequency of dosing in patients who had not responded to the longer dose regimens increased the overall proportion of patients who responded to lanreotide.

IV.10.10.2.3 VI.3.2.3 Study [redacted]

Study [redacted]) was an open label 12 month study conducted in 116 acromegalic patients in order to evaluate safety and efficacy of oanreltide Microparticles on clinical symptoms and biological parameters. Patients receiving somatostatin analogues at inclusion underwent a two week wash out period for immediate release forms or a one month wash out for prolonged releases formulations. Each patient received one i.m. injection of lanreotide Microparticle every 14 days, this was increased to every 10 days if GH and/or IGF-1 levels were not normalised. At the end of the study mean GH and IGF01 levels decreased significantly. The median GH concentration in the ITT population decreased from 10.66 ng/ml at baseline to 4.86 ng/ml at the LVA. By month 12, 42.4% of patients had normalised GH levels (≤ 5ng/ml) and 32.6% had normalised IGF-1(<450ng/ml), while 42.3% of patients had normalised levels of both GH and IGF-1. At the last evaluation, 11% of patients were totally asymptomatic.

IV.10.10.3 VI.3.3 Discussion of primary efficacy study results

Overall at least 680 acromegaly patients have been treated with lanreotide in the studies presented in this application for the purposes of demonstrating efficacy of either the Microparticle or Autogel formulation in acromegaly. 499 of these have been included in either the two pivotal lanreotide Autogel studies or the three key lanreotide Microparticle studies. A comparable number of males to females were treated in all of these studies with the age range being between 18 and 83 years of age.

In the pivotal lanreotide Autogel and key lanreotide Microparticles studies the primary and secondary endpoints have been discussed in detail in the Summary of Clinical Efficacy (Section 2.7.3). For the GH control at ≤2.5ng/ml, between 35.3% and 65.1% of patients treated with lanreotide Microparticles and up to 68% treated with lanreotide Autogel (Study [redacted]) reached this limit and were therefore considered to be controlled with regards to GH level (see Table 6). Briefly, for the less stringent endpoint of GH ≤5.0ng/ml, in the pivotal studies, up to 86% of patients treated with lanreotide Microparticles and up to 93% on lanreotide Autogel successfully reached this criterion. For the key lanreotide Microparticle studies only in study E45 52030 065 was this endpoint analysed. The mean percentage of patients with GH ≤5ng/ml at the last time point was 51.5% in this study.

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For normalised IGF-1, 50% of patients had normalised IGF-1 levels at the end of treatment with lanreotide Autogel and up to 52.4% of patients treated with lanreotide Microparticles. It should be noted that there were differences in the response rates between studies due to the method of age adjustment that was used, differences in assay or differences in dose regimen. Therefore a more conservative definition of IGF-1 normal may have been a result in some studies. It should also be noted that patients responded at the first time point assessed for each designated endpoint in all of the studies presented.

For the treatment goal of GH≤2.5.0ng/ml and normal IGF-1 levels up to 43% of patients reached this criterion having been treated with lanreotide Autogel and up to 53.6% with lanreotide Microparticles. For both GH and IGF-1 over time it was found that GH levels at baseline were inversely correlated with dose or dose frequency, i.e. patients with more severe disease needed either a greater dose or more frequent dosing depending on the formulation of lanreotide used.

Table 6: Comparison of the percentage of patients achieving primary endpoint results at Iva in the two pivotal Autogel and three key microparticle studies

Primary endpoint	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	% (n/N)	**%(n/N)**	**% (n/N)**	**% (n/N)**	**% (n/N)**	**% (n/N)**
Formulation	Microparticle	Microparticle	Microparticle	Microparticle	Autogel	Autogel
GH≤2.5 ng/ml	65.1 (54/83)	35.3 (6/17)	-	47 (62/132)	54 (71/131)	68 (83/123)
GH≤5ng/ml	-		51.5 (34/66)	86 (114/132)	81 (106/ 131)	93 (113/122)
Normalised IGF-1	52.4 (43/82)	31.6 (6/19)	40.4 (36/89)	45 (60/132)	50 (65/131)	50 (62/123)

It is difficult to compare GH and IGF-1 levels across studies due to difference in study design and objectives. However, the three key Microparticle studies clearly demonstrate that lanreotide reduces GH and IGF-1 levels in responder patients not controlled at study entry (see Tables 7 and 8). The extent of the reduction is dependent on severity of disease at inclusion.

Tables 7: Mean and median GH levels (ng/ml) overtime

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Visit		[redacted]	[redacted]	[redacted]
Baseline				
	N	19	85	66
	Median	8.95	5.12	10.66
	Mean±SD	23.91±26.07	10.20±15.08	14.30±11.56
	[min, max]	[2.6, 84.7]	[2.5, 89.0]	[5.0, 74.8]
LVA				
	N	19	83	65
	Median	3.56	1.98	4.86
	Mean±SD	5.70±6.52	4.80±16.24	7.06±7.21
	[min, max]	[0.3,23.9]	[0.3, 146.2]	[0.6, 35.6]

Table 8: Mean and median IGF-1 levels (ng/ml) overtime

Visit		[redacted]	[redacted]	[redacted]
Baseline				
	N	19	85	89
	Median	903	816.0	620.0
	Mean±SD	941.4±277.4	818.3±310.3	686.9±251.4
	[min, max]	[344, 1415]	[323, 1813]	[324, 1440]
LVA				
	N	19	84	88
	Median	432.0	338.5	437.5
	Mean±SD	530.2±306.0	420.9±242.0	458.3±273.1
	[min, max]	[107, 1365]	[80, 1194]	[78, 1832]

The studies using the lanreotide Autogel formulation clearly show that this reduction is maintained; indeed, for GH, further reductions are observed. Considering the similar pharmacokinetical mechanism of GH and IGF-1 reduction with lanreotide, it can be concluded that lanreotide Autogel will be similarly effective in patients not previously treated with lanreotide Microparticles or other somatostatin analogues.

For the majority of patients treated with both formulations few of the symptoms associated with acromegaly worsened during treatment. The majority of symptoms remained stable with some patients demonstrating improvements. Generally on lanreotide Autogel a greater number of patients remained at the stable intensity than with lanreotide Microparticles. In

five of the supportive studies improvements in symptoms were observes for: night sweats, joint pain, limb infiltration, headache, asthenia, perspiration, snoring and acral enlargement.

IV.10.11 VI.4 Supportive efficacy studies

IV.10.11.1 VI.4.1 Supportive lanreotide Autogel studies

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Lanreotide Autogel was investigated further in study [redacted]. This was a multicentre, comparative study to evaluate the efficacy and safety of seven repeated deep subcutaneous administrations of lanreotide Autogel (4x9mg followed by 3x 60, 90 or 120mg, depending on individual GH levels, at 28 day intervals), in acromegalic patients previously treated with Octreotide LAR 20mg in order to produce accurate clinical guidelines for the successful transfer of acromegaly patients. Out of the 12 patients that started the study, ten completed and were included in the PP population. At week 28, although all treatment groups still had slightly higher GH levels compared to baseline, nine (90%) patients were within the clinically accepted level for control of acromegaly. Despite the small patients population involved the data is adequate to conclude that lanreotide Autogel is effective in the treatment of acromegaly for patients previously treated with Octreotide LAR.

IV.10.11.2 VI.4.2 Supportive lanreotide Microparticle studies

A further seven supportive lanreotide Microparticle studies in acromegalics have also been presented in this application.

Of these one of the largest studies, that had a very similar outcome to [redacted], was a multicentre study ([redacted]) in acromegalic patients previously treated satisfactorily with octreotide. This study examined the effects of two dose regimes, as lanreotide Microparticles was administered every 10 days for the first month and every 14 days for the second and third months. Thereafter the dose (injection frequency) could be changed dependent upon GH levels. The results of treatment with lanreotide were statistically significant reductions of both variables and the clinical response was recorded as GH levels normalised in 47.6% (20/42) of patients, and IGF-1 was normalised in 28.3% (13/46) of patients. Individual analysis showed that the response to treatment, particularly in terms of GH, was highly dependent on baseline levels. Although baseline variability was high after six months treatment with lanreotide, only nine of 51 (18.7%) patients entered had GH levels of greater than 10ug/1. In addition, a comparison with end of octreotide treatment prior to the week's washout showed mean GH levels slightly higher at the end of lanreotide treatment although the median values were similar. Where implemented, an increase in the rate of administration from one injection per 14 days to one injection per 10 days brought about a clinically relevant further reduction in GH levels. Symptoms remained generally unchanged with lanreotide compared to end of treatment assessment with octreotide.

The efficacy of lanreotide was also investigated in a small study of eight patients with acromegaly conducted at Charing Cross Hospital, London ([redacted]). This group had not had any previous medical treatment and was treated for sic months, with one i.m. injection every 14 days. There was a pronounced reduction in IGF-1 by more than 35% in six out of eight patients and in GH levels of more than 50% in five out of eight patients. All eight patients had some improvement in symptoms although all patients also complained of adverse events related to the gastrointestinal system.

Another open label, single centre study of similar design allowed for the adjustment of the interval between doses, albeit towards the end of the evaluation ([redacted]). This study had one of the longer follow up periods (up to 56 weeks) and eight of nine patients had treatment changed during the last month from one injection every 14 days to one every 10 days. Unfortunately, this change was made far too late in the study to provide meaningful data on the biological effects of such dose adjustment. In contrast to the multicentre study [redacted], a comparison with octreotide was not an objective, hence making the results with lanreotide Microparticles more easily interpreted. As with the other studies, a GH level below 5ng/ml was considered as normalisation. This is a fairly stringent aim in a study with only one dosage of medication available especially since the biological results gained from any study of this type are dependent on baseline levels. In respect of the latter, the thresholds for reductions in GH and IGF-1 were 50% and 35% respectively. Biological data from this study were largely similar to other studies with a fixed treatment regime of one injection over 14 days and like other studies all patients had an improvement in symptoms.

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In general, these data show that lanreotide Microparticles provide adequate control of GH and IGF-1 levels especially since in both the [redacted]) and the E54 [redacted]) studies the hormone levels were only measured at the time of minimum plasma lanreotide levels – just prior to the next routine injection of lanreotide.

Retrospective comparisons with octreotide were attempted in two studies in which lanreotide was used as a continuation of octreotide with a therapeutic washout period. The duration of this washout period was seven days in one ([redacted]) and 14 days in the other ([redacted]). Despite the short plasma half life of octreotide, these washout periods were inadequate to allow primary biological variables to return to their pre-octreotide levels. Only the study [redacted] allowed a historical comparison with octreotide and the results showed clearly that both treatments provided similar biological control. The number of patients studies (n=16) in the [redacted] trial was insufficient to allow any meaningful comparison.

The only real test of comparative efficacy is a controlled comparative study allowing patients with newly diagnosed acromegaly to be randomised to treatment with either lanreotide or octreotide. Such a study would be very difficult to perform in a reasonable time frame due to the low incidence of acromegaly. In order to have sufficient statistical power, numbers would need to be very great. Even if one was to consider patients already on treatment, there might be practical or ethical considerations related to the duration of any washout period. Also, a placebo-controlled trial of efficacy would be difficult to justify on ethical grounds because of the availability of an active treatment. Thus, only open label, comparative studies are likely to be feasible in this indication.

However, despite these potential drawbacks, the company conducted an open study comparing lanreotide to octreotide in a parallel-arm design trial in acromegaly patients ([redacted]). In order to comply with clinical practice in treating acromegaly, physicians were permitted to titrate the dose of octreotide according to the GH response (doses from 50ug up to 500ug tds). For lanreotide, variation of the dose interval from one injection every 10-14 days was permitted by protocol. During the six month trial period, both treatment regimens produced similar improvements in biochemical parameters

(GH and IGF) and clinical symptoms. Between 55- 59% of patients had their GH levels "normalised" by treatment (to ≤ 5ng/ml). Taken overall, it appears that the results of treatment with lanreotide or octreotide are very similar but in terms of patient preference, 78% elected to carry on with lanreotide therapy after the formal trial.

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Surrogate biochemical parameters (eg GH, IGF-1) have previously been used as an index of efficacy for drug treatment of acromegaly and it is clear that, despite the noted deficiencies in some of the studies, lanreotide is effective in reducing these in most patients. In addition, there is no doubt that lanreotide resulted in a marked amelioration of most of the symptoms and the soft tissues signs of acromegaly. These results are similar to those seen with octreotide. Study [redacted] was a larger study in which patients' dose regimen could be adjusted after 12 weeks from every 14-days to every 10-days and then to every 7-days after another 12 weeks if the condition remained uncontrolled. Lanreotide Microparticles was again found to successfully suppress GH and/or IGF-1 levels in 51% of the evaluable patients with a reduction in the number of clinical symptoms reported of 38% (29 patients).

These supportive lanreotide Microparticle studies indicate that lanreotide is effective in ameliorating both the objective and subjective variables of acromegaly, not controlled by surgery. These results were obtained with a treatment regime of one injection of 30mg lanreotide Microparticles every 14 days with the option to adjust the dosing interval in accordance with the clinical or biochemical response. The results were maintained and generally improved with time as evidenced particularly in the study [redacted] and [redacted], an early evaluation after two weeks showed that efficacy was present very early in treatment. In all studies the three month date confirmed the maintenance of the relevant biological and clinical response and results from longer follow-up (12-18 months) showed not only a maintenance of efficacy but further improvements were noted in some individual responders. If there was no response, this rapidly became apparent and although a change in treatment regime did not allow an improvement in some, there were still a number of complete non-responders presumably related to tumours not expressing SSTR2 receptors. In conclusion, these studies were sufficient to demonstrate the objective and subjective efficacy of lanreotide, in the treatment of post-surgical active acromegaly.

VII. OVERVIEW OF SAFETY

IV.10.12 VII.1 Introduction

In this application safety data has been presented by individual study rather than as an integrated analysis of safety. This was because most of the relevant safety data came from only a small number of pivotal studies which gave a more accurate representation of data when interpreted separately. As lanreotide has been studied in several indications the decision was taken to present safety data from lanreotide studies in acromegalic patients, healthy volunteers and special populations only. Safety analyses from other indications with very different populations, including carcinoid tumours, variceal bleeding, AIDS-related diarrhoea and restenosis following coronary angioplasty are not presented.

The focus of the safety analysis is on two pivotal Autogel studies. Study E28 52030 709 investigate the switch from the widely marketed lanreotide Microparticle formulation of lanreotide to the lanreotide Autogel formulation. The second study, [redacted], was the

follow on study from [redacted] and involved the recruitment of patients who had completed [redacted]. Data are also presented on supportive studies with lanreotide Autogel and lanreotide Microparticles.

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IV.10.13 VII.2 Pivotal lanreotide Autogel studies

In each of the [redacted] clinical study reports the safety population was defined as consisting of all patients who had received at least on injection of either lanreotide Microparticles or lanreotide Autogel. In both of these studies AEs were coded according to the WHO ART dictionary. AEs were counted on a per patient basis. In cases where the same adverse event was reported on more than one occasion by a patient, the maximum intensity was used in the analyses (sever> not specified>moderate>mild). For drug relationship the most drug related category was used (probable>possible>not assessable>not related) – related adverse events were to include the causalities probable and possible. Post treatment adverse events were considered if they occurred within 28 days after the last dose of that patient's study medication.

In [redacted] a total of 144 patients received at least on run-in dose of lanreotide Microparticles:

- 73 patients were dosed at a 12 to 16 day dosing interval
- 42 patients at an 8 to 11 day dosing interval
- 28 patients at a 5 to 7 day dosing interval

133 of these patients went on to receive at least one run-in dose of lanreotide Autogel during the course of the second period:

a) 69 patients received 60mg lanreotide Autogel

b) 41 patients received 90mg

c) 23 patients received 120mg lanreotide Autogel

In the safety population, age ranged from 24 to 78 years and there was as expected similar percentage of males to females.

IV.10.14 VII.3 Adverse events

IV.10.14.1 VII.3.1 Study [redacted]

Overall, a similar percentage of patients reported AEs during lanreotide \Autogel treatment as during lanreotide Microparticle treatment (80%[N=133]) vs 75% [N=144] respectively). Overall, 52% of patients reported drug related adverse events during both treatment periods. Most AEs were mild in severity. A similar percentage of patients reported mild treatment related AEs during both treatment periods (47%[N=133] during lanreotide Autogel treatment vs. 51% [N=144] during Microparticles treatment).

As expected, most AEs were gastrointestinal (42%[N=133] during lanreotide Autogel treatment vs. 56% [N=144] during lanreotide Microparticles treatment).

The numbers of patients reporting AEs with an incidence of ≥5% are summarised for the safety population in Table 9 below.

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Table 9: Number of patients with AEs>5% in study [redacted]

Adverse Event	Lanreotide Microparticles N=144 N(%)	Lanreotide Autogel N=133 N(%)
Any AE	108 (75)	107(80)
Diarrhoea	55(38)	38(29)
Abdominal pain	31(22)	23(17)
Nausea	26(18)	12(9)
Constipation	15(10)	13(10)
Hyperglycaemia	5(3)	11(8)
Headache	9(6)	5(4)
Gallbladder sludge	4(3)	8(6)
Flatulence	3(2)	7(5)
Vomiting	7(5)	3(2)
Cholelithiasis	2(1)	7(5)
Hyperphosphataemia	4(3)	6(5)
Hyponatremia	4(3)	7(5)

IV.10.14.2 VII.3.2 Study [redacted]

In study E28 52030 710 a total of 130 patients, all of whom had completed study [redacted] 709, received at least one dose of lanreotide Autogel and were incorporated in to the safety population. In the safety population age ranged from 25 to 77 years and there were a comparable number of males to females. 123(95%) patients reported AEs. A similar percentage of patients reported AEs for each of the 60, 90, and 120mg doses. The majority of patients (92(71%)) reported mild AEs, with only one patient reporting a severe adverse event which was considered related to study medication (vomiting).

The most common AEs included; diarrhoea, abdominal pain, cholelithiasis and gall bladder sludge. There was no clear dose relationship for any of the frequently occurring AEs, with the exception of cholelithiasis, which occurred in 10% patients at 60mg, 15% patients at 90mg and 21% patients at 120mg. This was as expected as a disposition for gall bladder disorders has already been noted for this drug class, and recommendations for screening of patients undergoing treatment have been made in the proposed SmPC.

The number of patients reporting AEs with an incidence of ≥5% are summarised for the safety population in Table10 below.

Table 10: Number of patients with AEs>5% in study [redacted]

Adverse Event	**Lanreotide Autogel (all doses)**

	N=133 **N(%)**
Any AE	123(95)
Diarrhoea	43(33)
Abdominal pain	34(26)
Cholelithiasis	21(16)
Hyperglycaemia	21(16)
Gallbladder sludge	19 (15)
Constipation	18(14)
Hyponatremia	18(14)
Nausea	15(12)
Vomiting	13(10)
Hyperphosphataemia	12(9)
Sgot increased	12(9)
Headache	10(8)
Arthralgia	9(7)
Hyperkalaemia	9(7)
Surgical intervention	9(7)
Bilirubinaemia	8(6)
Flatulence	8(6)
Rhinitis	8(6)
Urinary tract infection	8(6)
Renal calculus	7(5)
Bronchitis	6(5)
Pharyngitis	6(5)

IV.10.14.3 VII.3.3 Gall bladder ultrasound

In these pivotal studies patients also underwent a gall bladder ultrasound. Overall the numbers and percentages of patients with either lithiasis or sludge were similar at baseline, at the end of treatment with lanreotide Microparticles and at the end of treatment with lanreotide Autogel at fixed doses. The incidence of lithiasis showed a slight increase from baseline levels over the course of treatment with lanreotide Autogel at titrated doses in study [redacted]. However, it should be noted that these comparisons are made between two time-points a year apart in treatment, from the end of the previous study ([redacted]) to the end of the study [redacted]. During this period it is to be expected that within a group of patients on treatment gall bladder status may worsen. Further analysis of the results of study [redacted] illustrates that out of the 130 patients recruited most of the patients with gall bladder disorder already showed symptoms, of either lithiasis or sludge, following treatment with the Microparticle formulation (32 patients), before the start of the study [redacted]. Eighteen patients developed gall bladder disorders related to the course of treatment with Lanreotide Autogel in this study. The incidence of these disorders was not found to be any greater than that observed previously with other treatments. There was also no relationship between these occurrences and the titrated dose of Lanreotide Autogel. It was therefore concluded that the incidence of gall bladder complications bore no relationship to the formulation of Lanreotide Autogel treatment. The incidence of sludge was comparable at all time points.

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IV.10.14.4 VII.3.4 Local tolerance

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Lanreotide appears to have good local tolerance in most patients. Similar percentages of patients with mild or moderate pain, redness and itching at the injection site were reported 30 minutes after dosing with each of the formulations. None of these were quoted a severe. A higher percentage of patients had indurations 30 minutes after injection with lanreotide Autogel (14% to 19%) compared with lanreotide Microparticles in study [redacted] (5% to 9%). However, by one dosing interval after injection of both formulations no clinically significant differences were observed in the percentage of patients reporting signs or symptoms at the injection site. Furthermore, the frequency of reports of local injection site reactions was less after three injection of lanreotide Autogel than after one injection in this study. The lack of spontaneous reports of local application site reactions in the clinical trial setting was noteworthy, and shows the lanreotide Autogel is well tolerated locally.

A Phase I study ([redacted]) was conducted to explore whether there was a preferred site for subcutaneous injection of lanreotide Autogel. In this study, healthy volunteers were injected over the deltoid, in the abdomen or in the buttock by the deep subcutaneous route at three different doses (60mg, 90mg and 120mg). 24 hours after the injection, palpable induration at the injection site was recorded in 17/27 subjects – 8 subjects injected in the arm, 8 subjects injected in the abdomen and 1 subject injected in the buttock. Forty two days after the injection, induration was observed in 20/27 subjects – seven in the arm, nine in the abdomen and 4 in the buttock. These palpable indurations were asymptomatic. The pharmacokinetics of lanreotide were no different in those subjects who developed a palpable induration compared with those who did not. There was no apparent relationship between the presence or absence of an induration, and the incidence of adverse events.

Because some of these local tissue reactions appeared persistent, the sponsor undertook a retrospective ultrasound examination of the injection site in [redacted]. Well defined oval or round echogenic images were found at the injection site 633 (median) days after dosing in 6/19 volunteers who consented to this follow up study. All these subjects were symptomatic. The relevance of this finding is difficult to assess, as it was not confirmed that any of these echogenic images actually represented a tissue reaction to the injection, and secondly, no baseline assessments were done, hence no comparison is available. In conclusion, and as discussed in the pharmacotoxicological Expert Report, it does appear that some animal species may develop a persistent granulomatous tissue reaction to the subcutaneous injection of lanreotide Autogel. The occurrence of a local tissue reaction is not accompanied by any systemic adverse events, either in the human studies, or apparently in the animal studies either. From the data available on the effects at different sites of injection, we can conclude that the buttock is the preferred site for deep subcutaneous injection.

IV.10.15 VII.4 Serious adverse events

For the pivotal lanreotide Autogel studies, no deaths were reported during [redacted] and there were two deaths reported for study [redacted]. One during the study (infection of left hip prosthesis, abscess of hip joint) and one afterwards (enlarged nymph node left axial due to mammary carcinoma). Neither was considered related to the study medication.

IV.10.15.1 VII.4.1 Study [redacted]

In study [redacted], four (3%) patients had SAEs considered unrelated to study medication having been dosed with lanreotide Microparticles. These consisted of back pain, neoplasm, bronchitis and haemoptysis. Two of these patients were withdrawn as a result of these AEs (neoplasm and haemoptysis). One patient reported an SAE during treatment with lanreotide Autogel, and inflicted injury. One patient withdrew during treatment with lanreotide during treatment with lanreotide Autogel due to a combination of drug related AEs (hot flushes, abdominal pain, diarrhoea, nausea and tenesmus).

Redacted according to Section 40, FOI Act

IV.10.15.2 VII.4.2 Study [redacted]

In study [redacted], 24 patients reported 29 SAEs. None patients dosed with 60mg, four patients with 90mg and eleven patients with 120mg of lanreotide Autogel Two patients had SAEs that were considered possibly or probably related to study medication – biliary pain and gall bladder extraction. All other SAEs were considered unrelated to study medication. Four patients reported treatment emergent AEs that caused their withdrawal from the study. One patient died and two had unrelated SAEs (cerebrovascular disorder and somnolence). The final patient withdrew due to a non- serious related AE (injection site reaction).

IV.10.15.3 VII.4.3 Laboratory evaluations

In the clinical laboratory evaluations of both [redacted] and [redacted] there were no clinically significant changes in any haematology parameter over the course of the treatments. There were also no clinically significant changes in any of the biochemistry parameters analysed during the studies and results were comparable across treatments and doses. One exception was the incidence of hyperglycaemia; five patients reported hyperglycaemia during treatment with lanreotide Microparticles, eleven patients during treatment with lanreotide Autogel at fixed doses and 21 patients during treatment with lanreotide Autogel at titrated doses in study [redacted]. It is important to note here that the condition of hyperglycaemia is a known risk factor of the acromegaly disease. Blood glucose should be monitored in patients treated with lanreotide and this recommendation is made in the SmPC.

IV.10.15.4 VII.4.4 Supportive Autogel study

There was only one supportive study submitted to provide additional safety data on lanreotide Autogel. The UK study [redacted] examined 12 patients in a switching study from the somatostatin analogue Octreotide LAR to lanreotide Autogel. 12 patients were included in the safety population of these six (50%) reported at least one AE (21 AEs were reported in total). As in the pivotal lanreotide Autogel studies, lanreotide Autogel was generally well tolerated with most AEs being mild in nature. The most common adverse events reported were injection site reactions (4 patients) or sweating (2 patients).

IV.10.16 VII.5 Non pivotal studies

IV.10.16.1 VII.5.1 Adverse events

Adverse event data has been presented for three key lanreotide Microparticle studies that have been submitted to provide additional supporting data to the safety of lanreotide using the lanreotide Microparticle formulation only. As with the Autogel formulation, lanreotide

Microparticles was generally well tolerated by most patients. The adverse event profile seen in these lanreotide Microparticle studies reflects that seen with the lanreotide Autogel formulation. Redacted according to Section 40, FOI Act

In study [redacted], 19 (100%) patients reported AEs, the most common of which was diarrhoea, reported by 11 (57.9%) of patients (se Table 2.7.4.2-6 in the clinical summary of safety). In study [redacted], 81 (95.3%) patients reported AEs, the most common of which was again diarrhoea (54 patients [63%]) (see Table 2.7.4.2-7 in the clinical summary of safety). Study [redacted] involved patients switched from Octreotide LAR treatment to lanreotide Microparticles. 89 (76.7%) of patients reported AEs in this study and the most common AE reported was cholelithiasis in 16 (13.8%) patients (see Table 2.7.4.2-8 in the clinical summary of safety).

IV.10.16.2 VII.5.2 Serious adverse events and deaths

Of the non- pivotal studies (including the three key lanreotide Microparticle studies mentioned above together with the supporting lanreotide Microparticle acromegaly studies, healthy volunteer and pharmacokinetic studies) included in this application (15 studies with approximately 773 patients or volunteers), four patients died. Two deaths occurred in study [redacted] (one aneurysm and one unknown cause after the end of the study). The third death occurred in study [redacted] (myocardial infarction) and the final death occurred in study [redacted] (cause unknown). None of the four deaths in these key studies were considered related to the study medication. 100 patients reported other SAEs. 91 were reported during lanreotide Microparticle treatment and three were during treatment with lanreotide Autogel 60mg. The remaining SAEs did not have a dose or formulation reported. 28 of these SAEs were considered either possibly or probably related. The most common related AEs included abdominal pain, cholecystistis, cholelithiasis and headache.

A final search of pharmacovigilance database for other deaths and SAEs reported for all other studies not included in this application (25 studies with other formulations or doses and ongoing studies in acromegalic patients and healthy volunteers [see Table 2.7.4.1-1]} resulted in the occurrence of a further three deaths reported in patients undergoing lanreotide treatment. This included a pulmonary embolism, not considered related, and a myocardial infarction and hepatitis, causality given as not reported and not assessable respectively. A total of 139 SAEs were reported in these studies. Of these nine were classed as possibly related (one case each of diverticilitis crisis, abdominal pain, cholangitis, headache, hyperglycaemia, hyponatraemia, intestinal perforation, pancreatitis and thrombophlebitis) and seven were probably related (including two cases of pancreatitis and one case each of biliary pain, cholelithiasis, diarrhoea, face oedema and haemorrhage rectum). Similar SAEs were reported as seen previously.

VIII. BENEFITS AND RISKS CONCLUSIONS

Lanreotide Microparticles has been registered and supplied in over 40 countries and has demonstrated an acceptable efficacy and safety profile in clinical use. The new formulation of lanreotide Autogel has shown similar qualities in clinical trials. The results of the non

inferiority testing in the pivotal study [redacted] fulfilled the primary objective by showing that lanreotide Autogel was no less effective than lanreotide Microparticles in maintaining GH levels and in controlling IGF-1. Longer term treatment in patients for a further 12 months was associated with further improvements both in biological and clinical indicators of the acromegaly disease. The symptoms of acromegaly remained stable in the majority of patients being treated with either of the lanreotide formulations.

Redacted according to Section 40, FOI Act

The lanreotide Microparticle studies presented in this application clearly demonstrate that lanreotide reduces GH and IGF-1 levels in responder patients not controlled at study entry. Lanreotide Autogel studies show that this reduction is maintained during long term treatment with this new product. Considering the similar pharmacokinetic profiles of these two formulations and the well defined pharmacological mechanism of GH and IGF-1 reduction with lanreotide, there is every reason to believe that lanreotide Autogel will be similarly effective in patients not previously treated with lanreotide Microparticles or other somatostatin analogues. In general, patients should begin therapy at a dose of 60mg once per month. According to the individual patients response (as judged by a reduction in symptoms and/or a reduction in GH and IGF-1 levels) and the clinical judgement of the prescriber, this may be increased up to 120mg per month.

All AE data reported during lanreotide Microparticle treatment and during lanreotide Autogel treatment were similar in nature. In particular, no unexpected adverse reactions were reported. The pharmacological properties of lanreotide have been linked to a high incidence of gastrointestinal AEs, and the profile of gastrointestinal adverse events seen with lanreotide Autogel was very similar to that seen with lanreotide Microparticles.

The frequency of reports of local injection site reactions was less after three injections of lanreotide Autogel than after one injection. Periodic Safety Update Reports (PSUR) covering both the lanreotide Microparticle and Autogel formulations have been included in Module five of this application. These include early experience of the marketing of lanreotide Autogel which has been approved in 13 European countries and was first launched in December 2001. The side effect profile of the product is entirely in accordance with that expected for this prolonged release drug and seen in the clinical trials.

Lanreotide Autogel has advantages for both the clinician (longer duration of action, ready for use injection) and for the patient (reduced frequency of injection, deep subcutaneous injection). Like lanreotide Microparticles, lanreotide Autogel provides distinct improvement in the symptoms of acromegaly and has demonstrated a safety profile that is encouragingly acceptable in relation to the risk/ benefit ratio. The advantages of this ready to use formulation make it a significant addition to the treatments available for patients suffering from active acromegaly, in particular those patients who have failed to respond to optimal therapy with surgery and/ or radiotherapy.

IX. DISCUSSION

This is a good quality submission and there are no major objections.

The non-inferiority of lanreotide Autogel was demonstrated when given in equivalent doses to the currently licensed Somatuline LA 30 mg microspheres with respect to GH and IGF-1

levels in acromegalic patients. Also, the safety profile of lanreotide Autogel is similar to Somatuline LA.

X. CONCLUSIONS

The RMS recommends that the application be approved.

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

APPENDIX 1

VARIATIONS

This appendix contains additional information considered essential for the determination of this application

Assessment Report
Mutual recognition Procedure

Ipstyl LA 60, 90, 120mg Solution for Injection

Lanreotide Acetate

UK/H/0723/001-003

Applicant: Ipsen Ltd

Date: 14th December 2004

APPENDIX 1 - VARIATIONS

UK LICENCE No.:	**PL 06958/0020-22**
PRODUCT:	**Ipstyl LA 60, 90 and 120mg Solution for Injection**
ACTIVE(S):	**Lanreotide Acetate**
COMPANY:	**Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK**
EC ARTICLE:	**Full dossier, Article 8.3(i)**

[redacted]

Redacted according to Section 43, FOI Act

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

APPENDIX 2

ORIGINAL ASSESSMENT REPORT FOR SOMATULINE PR

This appendix contains additional information considered essential for the determination of this application

Somatuline PR

Lanreotide Acetate

PL 06958/0018

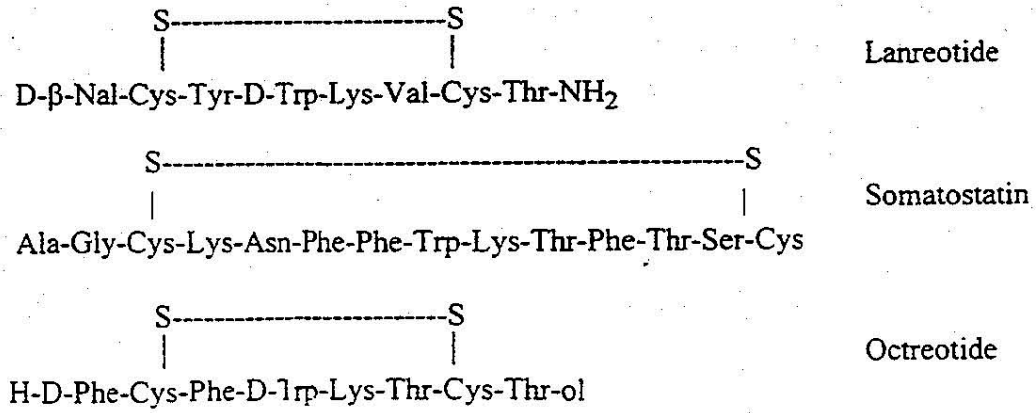
Date: May 1997

PART III - SOMATULINE PR (PL 10829/0006)

PRECLINICAL ASSESSMENT

INTRODUCTION

Somatuline PR is a prolonged release formulation of lanreotide acetate, a synthetic octapeptide with a biological activity similar to that of the naturally occurring hormone somatostatin. Lanreotide is characterised by the presence of a disulphide bridge and of a non-physiological amino acid, D-Trp, in the ring, which stabilises the molecule and results in a much longer duration of action in comparison to the natural hormone, somatostatin.



The active ingredient, lanreotide acetate, is encapsulated in microparticles composed of copolymer matrix derived from D,L-lactic and glycolic acid. The D,L-lactide/glycolide copolymer (50:50 lactide:glycolide) together with low levels (2%) of the lactic/glycolic copolymer are used to produce a prolonged release delivery system.

The proposed indications are for the treatment of acromegaly and the clinical symptoms associated with neuroendocrine (particularly carcinoid) tumours. The product is intended for intramuscular administration with a proposed dosing schedule of a single intramuscular injection of 30mg lanreotide every 14 days; but the frequency may vary depending on the patient's response.

The Expert Report, written by [redacted] is a very useful summary and critical analysis of the available data and is included in Appendix 1. Selected tabulated summaries of data for the repeat dose toxicity studies are also included in Appendix 1. However, the tabulated summaries for other areas of preclinical studies, particularly the reproductive toxicity studies, were either not altogether accurate and/or contained inappropriate data. The written summaries of these studies supplemented by tables of results from the original study reports have been used to compile the appendices for the areas of reproductive toxicity and mutagenicity.

Redacted according to Section 40, FOI Act

Most of the pivotal safety studies were conducted according to GLP.

PHARMACOLOGY (SEE EXPERT REPORT PAGE III-15)

The background and pharmacodynamics of lanreotide are well summarised in the Expert Report.

Briefly, binding of lanreotide to somatostatinergic receptors of the anterior pituitary, pancreas, and adrenal cortex is similar to native somatostatin but affinity for CNS receptors is reduced 1000-fold.

The pharmacological rationale for the use of lanreotide for the treatment of acromegaly is the inhibitory effect of lanreotide on the secretion of GH which has been demonstrated in normal male rats and male rats with transplanted tumours expressing somatostatin receptors, Cynomolgus monkeys and Merino rams. The inhibitory effect of lanreotide on GH secretion in rats was more potent and of a longer duration than that of native somatostatin and comparable to that of a currently licensed somatostatin analogue (octreotide - Sandostatin).

Limited pharmacodynamic data was provided in direct support of the indication for the treatment of clinical symptoms of carcinoid tumours. However, studies in rats and one study in dogs, showed that lanreotide may also modify those aspects of the physiology of the gastro-intestinal system which are modified by somatostatinergic mechanisms.

Lanreotide appears to have a less marked effect in rats on glucose-induced insulin secretion than native somatostatin and octreotide whereas its effect on glucagon secretion is similar to or greater than that of somatostatin. In rat models, lanreotide inhibits pentagastrin and histamine stimulated gastric acid secretion, slows intestinal transit time and inhibits PGE1-induced jejunal secretion more effectively than somatostatin. Lanreotide reduces caerulein-induced pancreatic hyperplasia by 27% when administered at 100ug/rat bid (SC) for 3 days and inhibits amylase secretion by 80-90% when injected at a dose of 1ug/kg (SC) immediately prior to induction of acute pancreatitis by ligation of the bile duct in rats.

A range of secondary pharmacology studies have been conducted (in vitro receptor binding, in vitro histamine release and in vivo studies on the CNS, autonomic nervous system, cardiovascular system, gastro-intestinal system, uro-genital system and analgesic activity). These studies were not conducted according to GLP but this assessor agrees with the author of the Expert Report that there is little justification for requiring repetition of the secondary pharmacology studies to GLP.

Receptor binding studies showed that lanreotide can also bind to opiate receptors although this was not felt to be important since lanreotide does not cross the blood-brain-barrier. However, lanreotide exhibits both anti-nociceptive and analgesic activity whereas somatostatin is either inactive or less active in the same animal models. Both somatostatin and lanreotide induce histamine release from mast cells in vitro and in vivo and a no-effect dose for this effect has not been established. Lanreotide is able to act as an anti-diuretic but only in the presence of vasopressin.

Biliary stasis is inducible in mice with both lanreotide and somatostatin and this effect has also been observed in clinical trials.

The findings of the pharmacology and secondary pharmacology studies are adequately reflected in warnings in the SmPC (Sections 4.4 and 4.8).

One drug interaction study was provided apparently because the interaction has been reported in man. Co-administration of lanreotide (SC) and cyclosporin A (IV or PO) to rats had no effect on the pharmacokinetic parameters for cyclosporin A.

PHARMACOKINETICS (SEE EXPERT REPORT PAGE III-22)

The pharmacokinetic data are well summarised and analysed in the Expert Report and the deficiencies in the studies have also been discussed.

In rats, lanreotide is rapidly absorbed and distributed when administered SC and bioavailability by this route is between 45-60%. In a tissue distribution in rats, negligible levels of radioactivity were found in the brain after SC administration of Iodine-125 labelled lanreotide. The drug is mainly eliminated by the liver via the bile, as seen with other somatostatin analogues, and there was evidence for enterohepatic recirculation. Using Iodine-125 radiolabelled lanreotide, no metabolites were observed in urine, bile or faecal samples. However, a range of metabolites were seen in rat urine, bile and faeces with tritium-labelled lanreotide although the interpretation of this data was complicated by evidence of extensive tritium exchange occurring and the formation of tritiated water and other volatile labelled products. The major route of elimination of the drug in rats after IV and SC administration is in the faeces via the bile, with low levels eliminated via the urine (<20%). In dogs, less than 4% of unchanged lanreotide was eliminated via the urine (radiolabelled mass balance study not conducted in dogs).

There is no information on metabolism in dogs or humans.

In vitro metabolism studies using trypsin, chymotrypsin and cathepsin B and various rat tissue homogenates provided evidence of the potential for exopeptidase metabolism of lanreotide.

The only toxicity study to include toxicokinetic monitoring was the 26-week IM study in dogs using the prolonged release formulation given once every 14 days. Plasma level data showed that exposures in dogs given the high dose (60mg/dog, every 14 days) were about 4-fold those obtained in patients (see Table 6 from the Expert Report).

Normalisation of single dose pharmacokinetic data after SC and IV administration to humans, rats and dogs, for a standard dose unit of 1ug/kg shows that plasma exposure, based on Cmax values, is 10-fold greater following a SC dose in humans than in rats with a ratio of 5 between exposure in humans and dogs (Table 4 and 5 from Expert Report). In repeat dose toxicity studies, rats have received SC doses up to 5000ug/kg/day (as 2 daily SC bolus injections) for 26 weeks and dogs have received

Expert Report Tables 4, 5, 6

Table 4: Pharmacokinetic parameters, normalised to a dose of 1 µg/kg, after bolus dosing with an immediate release formulation in humans, dogs and rats

Route of administration	Species	Cmax.mL^{-1}	AUC (µg.L^{-1}.h)
Intravenous	Human	-	3.44
	Rat	-	0.79
Subcutaneous	Human	1.53	3.10
	Dog	0.38	0.48
	Rat	0.13	0.42

Table 5: Comparative pharmacokinetics of lanreotide (IRF) in rats, dogs and human volunteers

Species	Route	Dose	Cmax (µg.L^{-1})	AUC (µg.L^{-1}.h)	t½ (hrs.)	Reference
Raf	i.v.	30 µg/kg		20.5	1.82	115, 116
		100 µg/kg		94.9	2.09	"
		300 µg/kg		219.3	6.56	"
		40 µg/rat (^{125}I)		56.3	5.3	119
		40 µg/rat (RIA)		64.3	7.8	"
	s.c.	30 µg/kg	5.3	11.7	1.16	117, 118
		100 µg/kg	11.7	43.6	1.73	"
		300 µg/kg	25.4	133.5	3.30	"
		40 µg/rat (^{125}I)	23.0	22.5		120
		40 µg/rat (RIA)	24.5	32.9		"
Dog	s.c.	200 µg/kg	75.2	95.5	10.00	121
Human	i.v.	7 µg/kg		24.1	1.44	92/PKS/14
	s.c.			$AUC_{0-\infty}$		
		7 µg/kg	12.3	19.2	1.9	Peraire 1992
		21 µg/kg	30.6	64.0	2.2	92/PKS/14
		42 µg/kg	58.2	146.9	2.3	"
	s.c. infusion		C_{ss}	AUC_{0-24h}		
		1000 µg/24 hr	1.7	34.3	2.0	Peraire 1992
		2000 µg/24 hr	3.4	71.2	1.9	91/PKS/29
		3000 µg/24 hr	4.9	107.0	1.3	"

Table 6: Comparative pharmacokinetics (i.m.) of lanreotide (SRF) in rats, dogs and human volunteers

Species	Route	Dose	Cmax1 (µg.L^{-1})	AUC_{0-t} (µg.L^{-1}.day)	MRT (days)	Reference
Rat						
Batch V001	i.m.	6 mg/kg	22.45	59.21	6.92	122, 123
Batch A002			24.76	71.97	6.01	124, 125
Dog	i.m.	3 mg/kg	23.25	95.32	5.43	126, 127
Human	i.m.	30 mg	6.8	24.63	7.98	92/PKS/49

Batch V001 non-lyophilised, Batch A002 lyophilised.

doses up to 10mg/kg/day for 45 days by continuous IV infusion. It would appear that both rats and dogs have been exposed to reasonable multiples of the systemic exposures obtained in patients given the prolonged release formulation, although the pattern of exposure is different.

TOXICOLOGY (SEE EXPERT REPORT PAGE III-30 AND PAGE III-44)

The acute, sub-acute and chronic toxicity studies are outlined in Table 7 (extracted from the Expert Report) and are well summarised and evaluated in the Expert Report in the context of the proposed clinical use of lanreotide.

The only study conducted with the prolonged release formulation of lanreotide administered intramuscularly once every 14 days was the 26-week dog study. In this study, 60mg (two X 30mg) IM injections were administered per dog in the high dose group. This study also included a satellite group given the high dose to monitor blood levels of lanreotide and hormone levels. Plasma levels at the highest dose in dogs were about 4-fold those obtained in patients given the recommended dose. Hormone analyses also demonstrated a dose-related decrease in clonidine-stimulated growth hormone secretion although basal GH activity was unchanged. There were no signs of systemic toxicity that would preclude the clinical use of the lanreotide in the formulation, doses and indications proposed. Granulomatous reactions at the injection site were seen except at the low dose, but these reactions had regressed in the recovery phase group.

There are no concerns about the toxicity of copolymer matrix used in the prolonged release formulation as similar copolymers have been used previously for other prolonged release formulations of hormone analogues intended for long-term treatment (eg GnRH analogues). These copolymers are synthetic polyesters of D,L-lactic and glycolic acids which are biocompatible and biodegradable by hydrolysis to the component acids which are normal endogenous compounds.

The remaining repeat dose toxicity studies in rats and dogs used an immediate release formulation administered by SC or IV injection or by continuous IV infusion. The doses in the SC studies were limited by local irritant effects. Although none of these studies included toxicokinetic monitoring, the 45 day continuous IV infusion study in dogs using doses up to 10mg/kg/day gives reassurance regarding the lack of unacceptable systemic toxicity due to lanreotide at the proposed clinical dose.

The effects observed in the continuous IV infusion study in dogs (gastro-intestinal disturbances, decreased glucagon, decreased circulating levels of thyroxine, testosterone and LH, and testicular atrophy/degeneration) were attributed to exaggerated pharmacological effects mediated by somatostatinergic receptors.

Daily SC administration of doses up to 120ug/kg/day for 2 years produced dose-dependent decreases in glucagon levels in rats and in glucose and insulin in dogs but without any other evidence of systemic toxicity.

Table 7: Acute, subacute and chronic toxicity studies

STUDY TYPE	SPECIES	DOSE	FINDINGS	REF.
Acute, s.c.	Mouse Rat	0.8, 600, 900, 1200 $mgkg^{-1}$ 0.8, 1500 $mgkg^{-1}$	$LD_{50} > 1200$ $mgkg^{-1}$ $LD_{50} > 1500$ $mgkg^{-1}$	1 - 4
Acute, i.v.	Mouse Rat	0.8, 30, 100, 120, 135, 150, 180 $mgkg^{-1}$ 3, 6, 24, 48, 60, 75 $mgkg^{-1}$	$LD_{50} \geq 135$ $mgkg^{-1}$ $LD_{50} > 48$ $mgkg^{-1}$	5 - 10
Subacute, s.c., 5 days	Mouse	800 $\mu gkg^{-1}day^{-1}$ Single injection	No signs of toxicity.	11, 12
Subacute, s.c., 6 weeks	Rat	4, 40, 200 $\mu gkg^{-1}day^{-1}$ Single injection	Glucagon levels reduced. Local reactions at injection sites. 40 μgkg^{-1} "no-effect" level. Decreased weight gain.	13, 14
Subacute, s.c., 6 weeks	Dog	4, 40, 200 $\mu gkg^{-1}day^{-1}$ Single injection	Glucose levels reduced. 40 μgkg^{-1} "no-effect" level. Local reaction at injection site.	15, 16
Subacute, i.v., dose finding	Dog	2.5, 5, 10, 20, 25 $mgkg^{-1}day^{-1}$ Continuous infusion	Decreased body weight, loose stools. Changes at injection site.	17, 18
Subacute, i.v., 45 days	Dog	0.4, 4, 10 $mgkg^{-1}day^{-1}$ Continuous infusion	No deaths; various systemic effects, including testicular atrophy with related decreases in testosterone and LH levels.	19, 20
Chronic, s.c., 26 weeks	Rat	200, 1000, 5000 (reduced to 2000) $\mu gkg^{-1}day^{-1}$ 2 daily injections	No deaths; local tolerance poor leading to reduction in dose in 5000μgkg^{-1} group; reduction in body weight gain and food consumption.	21 - 23
Chronic, i.m., 26 weeks	Dog	1.00-1.62, 3.35-4.98, 6.26-9.95 $mgkg^{-1}$ once every 2 weeks Two injections per administration	Local lesions at injection sites; reduction in body weight gain in intermediate and high dose groups	24, 25
Chronic, s.c., 2 yrs	Rat	8, 40, 120 $\mu gkg^{-1}day^{-1}$ Single injection	Local lesions at injections sites; dose-related decrease in glucagon levels; decrease in weight gain in high-dose males. "No effect" level 40 $\mu gkg^{-1}day^{-1}$.	26, 27
Chronic s.c., 2 yrs.	Dog	8, 40, 120 $\mu gkg^{-1}day^{-1}$ Single injection	Serum insulin levels decreased; high-dose females showed slightly reduced body weight gain; reduced blood glucose levels. "No effect" level 40 $\mu gkg^{-1}day^{-1}$.	28, 29

MUTAGENICITY (SEE EXPERT REPORT PAGE III-37 AND PAGE III-60)

Lanreotide was subjected to a battery of standard genotoxicity studies (reverse mutations in bacteria, mouse lymphoma assay, in vitro chromosomes aberration assay in human peripheral lymphocytes, mouse micronucleus assay by SC administration). In addition, the potential for inhibition of testicular DNA synthesis and DNA repair was assessed in mice and rats (IV and IP administration).

The standard studies were conducted to GLP and according to protocols deemed acceptable at the time the studies were conducted (1987-1993). The potential to induce reverse mutations in bacteria and chromosome aberrations in cultured human lymphocytes was examined on two separate occasions.

Although the results of the in vitro studies were not clearly negative and there were several isolated positive results, this assessor agrees with the overall conclusion of the author of the Expert Report that "there was no consistently reproducible evidence of any genotoxic potential in these assays. It can therefore be concluded that lanreotide can be considered as a non-genotoxic molecule."

The in vivo mouse micronucleus assay and testicular DNA synthesis and repair assay gave negative results. However, the micronucleus assay used doses up to 24mg/kg SC, a dose which induced no overt toxicity and was lower than the positive control dose of 40mg/kg cyclophosphamide. These doses of lanreotide apparently represented at least a 700-fold multiple of the human therapeutic dose proposed at the time the study was conducted; however, the proposed human dose is now 30mg IM every 14 days. In view of the lack of clearly reproducibly positive results in vitro, and the structure of lanreotide, it would not seem reasonable to request the Company to repeat the mouse micronucleus assay using higher doses of lanreotide.

CARCINOGENICITY (SEE EXPERT REPORT III-39)

Conventional rodent carcinogenicity bioassays using maximum tolerated doses have not been conducted with lanreotide although the treatment duration for acromegaly would strictly warrant carcinogenicity studies.

However, lanreotide has been administered by daily SC injection to groups of 25 male and 25 female rats for up to 2 years at doses up to 120ug/kg/day (at which systemic exposure can be estimated to be approximately 4-fold (???) that which may be anticipated in patients. There were no increases in the incidence of neoplastic findings in this study.

The assessor agrees with the conclusion of the author of the Expert Report that "whilst use of Somatuline PR is restricted to the treatment of acromegaly, when the secretion of growth hormones is not normalised after surgery and/or radiation therapy, and for treatment of clinical symptoms of carcinoid tumours than it is reasonable not to make the conduct of rodent carcinogenicty studies a pre-requisite to the granting of marketing authorisations."

REPRODUCTIVE TOXICITY (SEE EXPERT REPORT III-35 AND III-81)

Lanreotide is contraindicated in pregnancy and lactation.

The SPC statement on Pregnancy and Lactation (Section 4.6) states "Studies in animals showed transitory growth retardation of offspring prior to weaning. Although no teratogenic effects have been observed in animals, in the absence of clinical experience, lanreotide must not be administered to pregnant or lactating women."

Reproductive toxicity studies provided included a fertility and general reproductive performance study in the rat and teratology studies in the rat and rabbit. The fertility study used the prolonged release formulation administered at doses up to 10mg/kg IM every 2 weeks and 30mg/kg SC every 2 weeks. The teratology studied employed an immediate release formulation and employed daily SC doses up to 2000ug/kg (2 daily injections of 1000ug/kg) in rats and rabbits. A peri-postnatal study in rats has not been conducted. However, this omission is acceptable in view of the proposed clinical indications and the contra-indication in pregnancy and lactation.

There were no clear adverse effects on fertility or general reproductive performance although effects on male gonads were observed (atrophic and degenerative changes). There were four pairs of rats in the high dose group that did not prove fertile and this was considered to be possibly indicative of slightly reduced fertility. Similar atrophic/degenerative effects on male gonads were observed in the 45-day continuous IV infusion study in dogs and were attributed to effects on reproductive hormone levels induced by lanreotide (decreased levels of testosterone and LH).

In the teratology studies there was an increased incidence of ovarian cysts in rats given 2 X 1000ug/kg/day and possibly in rabbits (one low dose rabbit and one high dose rabbit had an ovarian cyst). This finding was not discussed further and the clinical relevance is unclear. A dose-related incidence of total resorption in rabbits was observed at 2 X 225 and 2 X 1000ug/kg/day, doses which caused maternal toxicity. There was no clear evidence of teratogenic activity. However, the interpretation of the reproductive toxicity studies is complicated because lanreotide and other somatostatin analogues will perturb reproductive physiology through modulation of the secretion of pituitary hormones.

ENVIRONMENTAL RISK ASSESSMENT (PAGE III-96)

A Phase 1 environmental assessment has been completed which indicates that the proposed use of Somatuline PR will not lead to entry into the environment at levels which would trigger the need for more detailed assessment of the potential for risk to the environment.

CONCLUSIONS

The preclinical data do not indicate any safety hazard for the use of lanreotide in the proposed prolonged release formulation, dose and clinical indications.

The findings in the toxicological evaluation programmed are adequately reflected in the SmPC (eg effects on glycaemic control). Section 5.3 of the SmPC (Preclinical safety data) is acceptable.

[redacted]

MAY 1997

Redacted according to Section 40, FOI Act

Medicines and Healthcare products Regulatory Agency

Safeguarding public health

APPENDIX 3

ORIGINAL ASSESSMENT REPORT FOR SOMATULINE AUTOGEL

This appendix contains additional information considered essential for the determination of this application

Somatuline Autogel 60, 90 and 120mg

Lanreotide Acetate

EC 65/65 Article 4.8

Date: May 2001

Market Towers 1 Nine Elms Lane
Vauxhall London SW8 5NQ

MARKETING AUTHORISATION APPLICATION (ABRIDGED)

ASSESSMENT REPORT

NUMBER: **PL: 10829/0008-10**

APPLICANT: Ipsen Biotech

ADDRESS: Ipsen Ltd,
Kensington Centre,
66 Hammersmith Road,
London W14 8UD.

AGENCY ASSESSORS:

PHARMACEUTICAL: [redacted]

PRE-CLINICAL: [redacted]

CLINICAL: [redacted]

Redacted according to Section 40, FOI Act

REPORT COMPLETED: May, 2001

PL No:****PLNO**********
Holder:***HOLDER**********
Formulation No:***FORMNO

Licensed name(s): **MORE**
LN1********
LN2********
LN3********
LN4********
LN5********

PART III

TOXICOLOGICAL AND PHARMACOLOGICAL TESTS

LICENCE No:	**PL's 10829/0008-10**
PROPRIETARY NAME:	**Somatuline Autogel 60 / 90 / 120mg**
COMPANY NAME:	**Ipsen Biotech**
EC ARTICLE:	**EC 65/65 Article 4.8**
ACTIVE INGREDIENT(S):	**Lanreotide acetate**
LEGAL STATUS:	**POM**

V PRECLINICAL ASSESSMENT

V.1 INTRODUCTION

Lanreotide AUTOGEL® is a prolonged-release formulation of lanreotide acetate available in three strengths, 60, 90 and 120 mg. The active ingredient is presented in a supersaturated aqueous solution in a sterile single-dose syringe. The product is administered (volume $\leq$ 0.5 ml) by deep *sc* injection. The intended indications are the treatment and symptomatic relief of acromegaly, and for the treatment of symptoms associated with neuroendocrine tumours. The maximum initial dose is 120 mg every 28 days.

This application is a line extension made under Article 4.8a(i), lanreotide PR 30 mg being a well-established product marketed as Somatuline, Somatulina or Ipstyl for the same indications since 1994 (in France initially). The licensed product contains a microparticulate polylactide-co-glycolide formulation of the acetate salt (30 mg) for *im* injection.

The preclinical expert report for this application, written by [redacted] (independent consultant) provides a detailed review of the toxicological information.

Redacted according to Section 40, FOI Act

V.2 PRECLINICAL COMMENT

Lanreotide, a synthetic octapeptide analogue of somatostatin, exhibits high affinity for somatostatin Type 2 and Type 5 receptors present in the pituitary gland and the pancreas, as well as in growth hormone (GH)-secreting pituitary tumours. Thus, it has a relatively specific inhibitory effect on

GH secretion making it suitable for the treatment of acromegaly (caused by hypersecretion of GH from a pituitary adenoma).

As is appropriate for this line-extension product, the preclinical studies have been restricted to evaluations of pharmacokinetics and local tolerance.

V.2.1 Pharmacokinetics

Two studies have been undertaken in the dog with *im* administration. Lanreotide acetate *iv* was used as a comparator in one study. The bioavailability of lanreotide was 91-93% and 95% of the peptide was released over 90-150 days. The studies were characterised by initially rapid, followed by a regular, smooth and sustained release of lanreotide from the depot injection. In one study there was a moderate initial "burst" effect, whilst this was absent in the other study.

V.2.2 Local Tolerance

A series of studies have been conducted mainly in the rabbit, but also in the minipig and monkey. Local tolerance following single or repeated *im* administration in the rabbit was assessed in two studies over 99-150 days. Clinical effects were generally minimal, localised mild induration being observed in the repeated-dose study. Histopathological examination revealed the presence of amorphous particulate material (presumably precipitated lanreotide) and a variety of inflammatory reactions of a type associated with foreign body-type responses, *eg* initial acute polymorph response evolving into giant cell infiltration and fibrosis with some necrosis, but only of adjacent muscle cells.

Single- and repeated-dose *sc* administration of the product, again being followed over periods of 99-150 days, produced a similar but less marked foreign body inflammatory response.

Administration by the *sc* route to the rabbit, minipig and monkey produced an acute inflammatory response in all species, which was of lowest intensity in the rabbit.

V.3 DISCUSSION

The kinetic profile of the drug was confirmed in the dog to be appropriate for a sustained-release product. Local inflammatory responses of a slight-to-mild type following *sc* administration were seen in three species and are not unexpected for this kind of preparation where the drug has the potential to be present in particulate form in the tissues for several months

The preclinical kinetic and local tolerance characteristics of Lanreotide AUTOGEL® are supportive of its clinical use.

V.3.1 SPC

Sections 4.6, 5.1 and 5.3 are acceptable.

V.4 CONCLUSION

The preclinical data provided support the grant of a marketing authorisation for Lanreotide AUTOGEL®.

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