ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SANDOSTATIN and associated names (see Annex I) 0.05 mg/1 ml ampoules, solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion)
SANDOSTATIN and associated names (see Annex I) 0.1 mg/1 ml ampoules, solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion)
SANDOSTATIN and associated names (see Annex I) 0.5 mg/1 ml ampoules, solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion)
SANDOSTATIN and associated names (see Annex I) multidose vials 1 mg/5 ml (0.2 mg/ml), solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion)

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

For the full list of excipients, see section 6.1.

[To be completed nationally]

3. PHARMACEUTICAL FORM

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic control and reduction of growth hormone (GH) and IGF-1 plasma levels in patients with acromegaly who are inadequately controlled by surgery or radiotherapy. Sandostatin is also indicated for acromegalic patients unfit or unwilling to undergo surgery, or in the interim period until radiotherapy becomes fully effective.

Relief of symptoms associated with functional gastro-entero-pancreatic (GEP) endocrine tumours, e.g. carcinoid tumours with features of the carcinoid syndrome (see section 5.1).

Sandostatin is not an anti-tumour therapy and is not curative in these patients.

Prevention of complications following pancreatic surgery.

Emergency management to stop bleeding and to protect from re-bleeding owing to gastro-oesophageal varices in patients with cirrhosis. Sandostatin is to be used in association with specific treatment such as endoscopic sclerotherapy.

Treatment of TSH-secreting pituitary adenomas:
- when secretion has not normalised after surgery and/or radiotherapy;
- in patients in whom surgery is inappropriate;
- in irradiated patients, until radiotherapy is effective.

4.2 Posology and method of administration

Posology

Acromegaly
Initially 0.05 to 0.1 mg by subcutaneous (s.c.) injection every 8 or 12 hours. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH <2.5 ng/mL; IGF-1 within normal range) and clinical symptoms, and on tolerability. In most patients, the optimal daily dose will be 0.3 mg. A maximum dose of 1.5 mg per day should not be exceeded. For patients on a stable dose of Sandostatin, assessment of GH should be made every 6 months.

If no relevant reduction in GH levels and no improvement in clinical symptoms have been achieved within 3 months of starting treatment with Sandostatin, therapy should be discontinued.

Gastro-entero-pancreatic endocrine tumours
Initially 0.05 mg once or twice daily by s.c. injection. Depending on clinical response, effect on levels of tumour-produced hormones (in cases of carcinoid tumours, on the urinary excretion of 5-hydroxyindole acetic acid), and on tolerability, dosage can be gradually increased to 0.1 to 0.2 mg 3 times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses have to be adjusted individually.

In carcinoid tumours, if there is no beneficial response within 1 week of treatment with Sandostatin at the maximum tolerated dose, therapy should not be continued.

Complications following pancreatic surgery
0.1 mg 3 times daily by s.c. injection for 7 consecutive days, starting on the day of surgery at least 1 hour before laparotomy.

Bleeding gastro-oesophageal varices
25 micrograms/hour for 5 days by continuous intravenous (i.v.) infusion. Sandostatin can be used in dilution with physiological saline.

In cirrhotic patients with bleeding gastro-oesophageal varices, Sandostatin has been well tolerated at continuous i.v. doses of up to 50 micrograms/hour for 5 days.

Treatment of TSH-secreting pituitary adenomas
The dosage most generally effective is 100 micrograms three times a day by s.c. injection. The dose can be adjusted according to the responses of TSH and thyroid hormones. At least 5 days of treatment will be needed to judge the efficacy.

Use in the elderly
There is no evidence of reduced tolerability or altered dosage requirements in elderly patients treated with Sandostatin.

Use in children
Experience with Sandostatin in children is limited.

Use in patients with impaired liver function
In patients with liver cirrhosis, the half-life of the drug may be increased, necessitating adjustment of the maintenance dosage.

Use in patients with impaired renal function
Impaired renal function did not affect the total exposure (AUC) to octreotide administered as s.c. injection, therefore no dose adjustment of Sandostatin is necessary.

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General

As GH-secreting pituitary tumours may sometimes expand, causing serious complications (e.g. visual field defects), it is essential that all patients be carefully monitored. If evidence of tumour expansion appears, alternative procedures may be advisable.

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalisation of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients could potentially restore fertility. Female patients of childbearing potential should be advised to use adequate contraception if necessary during treatment with octreotide (see section 4.6).

Thyroid function should be monitored in patients receiving prolonged treatment with octreotide.

Hepatic function should be monitored during octreotide therapy.

Cardiovascular related events

Common cases of bradycardia have been reported. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary (see section 4.5).

Gallbladder and related events

Octreotide inhibits secretion of cholecystokinin, resulting in reduced contractility of the gallbladder and an increased risk of sludge and stone formation. The incidence of gallstone formation with Sandostatin treatment is estimated to be between 15 to 30%. The incidence in the general population is 5 to 20%. Ultrasonic examination of the gallbladder before, and at about 6- to 12-month intervals during Sandostatin therapy is therefore recommended. The presence of gallstones in Sandostatin-treated patients is largely asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

GEP endocrine tumours

During the treatment of GEP endocrine tumours, there may be rare instances of sudden escape from symptomatic control by Sandostatin, with rapid recurrence of severe symptoms. If the treatment is stopped, symptoms may worsen or recur.

Glucose metabolism

Because of its inhibitory action on growth hormone, glucagon, and insulin, Sandostatin may affect glucose regulation. Post-prandial glucose tolerance may be impaired and, in some instances, the state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been reported.

In patients with insulinomas, octreotide, because of its greater relative potency in inhibiting the secretion of GH and glucagon than that of insulin, and because of the shorter duration of its inhibitory action on insulin, may increase the depth and prolong the duration of hypoglycaemia. These patients should be closely monitored during initiation of Sandostatin therapy and at each change of dosage. Marked fluctuations in blood glucose concentration may possibly be reduced by smaller, more frequently administered doses.

Insulin requirements of patients with type I diabetes mellitus therapy may be reduced by administration of Sandostatin. In non-diabetics and type II diabetics with partially intact insulin reserves, Sandostatin administration can result in post-prandial increases in glycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

Oesophageal varices

Since, following bleeding episodes from oesophageal varices, there is an increased risk for the development of insulin-dependent diabetes or for changes in insulin requirement in patients with pre-existing diabetes, an appropriate monitoring of blood glucose levels is mandatory.

Local site reactions

In a 52-week toxicity study in rats, predominantly in males, sarcomas were noted at the s.c. injection site only at the highest dose (about 8 times the maximum human dose based on body surface area). No hyperplastic or neoplastic lesions occurred at the s.c. injection site in a 52-week dog toxicity study. There have been no reports of tumour formation at the injection sites in patients treated with Sandostatin for up to 15 years. All the information available at present indicates that the findings in rats are species specific and have no significance for the use of the drug in humans (see section 5.3).

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

Depressed vitamin B12 levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B12 levels is recommended during therapy with Sandostatin in patients who have a history of vitamin B12 deprivation.

4.5 Interaction with other medicinal products and other forms of interaction

Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance may be necessary when Sandostatin is administered concomitantly (see section 4.4).

Dose adjustments of insulin and antidiabetic medicinal products may be required when Sandostatin is administered concomitantly (see section 4.4).

Sandostatin has been found to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

Concomitant administration of octreotide and bromocriptine increases the bioavailability of bromocriptine.

Limited published data indicate that somatostatin analogues might decrease the metabolic clearance of compounds known to be metabolised by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolised by CYP3A4 and which have a low therapeutic index should therefore be used with caution (e.g. quinidine, terfenadine).

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of octreotide in pregnant women, and in approximately one third of the cases the pregnancy outcomes are unknown. The majority of reports were received after post-marketing use of octreotide and more than 50% of exposed pregnancies were reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-1200 micrograms/day of Sandostatin s.c. or

10-40 mg/month of Sandostatin LAR. Congenital anomalies were reported in about 4% of pregnancy cases for which the outcome is known. No causal relationship to octreotide is suspected for these cases.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Sandostatin during pregnancy (see section 4.4).

Breastfeeding

It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breast-feed during Sandostatin treatment.

Fertility

It is not known whether octreotide has an effect on human fertility. Late descent of the testes was found for male offsprings of dam treated during pregnancy and lactation. Octreotide, however, did not impair fertility in male and female rats at doses of up to 1 mg/kg body weight per day (see section 5.3).

4.7 Effects on ability to drive and use machines

Sandostatin has no or negligible influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience dizziness, asthenia/fatigue, or headache during treatment with Sandostatin.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions reported during octreotide therapy include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported adverse reactions in clinical trials with octreotide administration were diarrhoea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycaemia and constipation. Other commonly reported adverse reactions were dizziness, localised pain, biliary sludge, thyroid dysfunction (e.g. decreased thyroid stimulating hormone [TSH], decreased total T4, and decreased free T4), loose stools, impaired glucose tolerance, vomiting, asthenia, and hypoglycaemia.

Tabulated list of adverse reactions

The following adverse drug reactions, listed in Table 1, have been accumulated from clinical studies with octreotide:
Adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 Adverse drug reactions reported in clinical studies

Gastrointestinal disorders	
Very common:	Diarrhoea, abdominal pain, nausea, constipation, flatulence.
Common:	Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces.

Nervous system disorders	
Very common:	Headache.
Common:	Dizziness.
Endocrine disorders	
Common:	Hypothyroidism, thyroid dysfunction (e.g. decreased TSH, decreased total T4, and decreased free T4).
Hepatobiliary disorders	
Very common:	Cholelithiasis.
Common:	Cholecystitis, biliary sludge, hyperbilirubinaemia.
Metabolism and nutrition disorders	
Very common:	Hyperglycaemia.
Common:	Hypoglycaemia, impaired glucose tolerance, anorexia.
Uncommon:	Dehydration.
General disorders and administration site conditions	
Very common:	Injection site reactions.
Common:	Asthenia.
Investigations	
Common:	Elevated transaminase levels.
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia.
Respiratory disorders	
Common:	Dyspnoea.
Cardiac disorders	
Common:	Bradycardia
Uncommon:	Tachycardia.

Post-marketing
Spontaneously reported adverse reactions, presented in Table 2, are reported voluntarily and it is not always possible to reliably establish frequency or a causal relationship to drug exposure.

Table 2 Adverse drug reactions derived from spontaneous reports

Immune system disorders
Anaphylaxis, allergy/hypersensitivity reactions.
Skin and subcutaneous tissue disorders
Urticaria
Hepatobiliary disorders
Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice.
Cardiac disorders
Arrhythmias.
Investigations
Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels.

Description of selected adverse reactions

Gastrointestinal disorders
In rare instances, gastrointestinal side effects may resemble acute intestinal obstruction, with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding.

The frequency of gastrointestinal adverse events is known to decrease over time with continued treatment.

Occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of Sandostatin s.c. administration, that is, by injecting between meals or on retiring to bed.

Injection site reactions
Pain or a sensation of stinging, tingling or burning at the site of s.c. injection, with redness and swelling, rarely lasting more than 15 minutes. Local discomfort may be reduced by allowing the solution to reach room temperature before injection, or by injecting a smaller volume using a more concentrated solution.

Metabolism and nutrition disorders
Although measured faecal fat excretion may increase, there is no evidence to date that longterm treatment with octreotide has led to nutritional deficiency due to malabsorption.

Pancreatic enzymes
In very rare instances, acute pancreatitis has been reported within the first hours or days of Sandostatin s.c. treatment and resolved on withdrawal of the drug. In addition, cholelithiasisinduced pancreatitis has been reported for patients on long-term Sandostatin s.c. treatment.

Cardiac disorders
In both acromegalic and carcinoid syndrome patients, ECG changes were observed such as QT prolongation, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases (see section 4.4).

4.9 Overdose

A limited number of accidental overdoses of Sandostatin in adults and children have been reported. In adults, the doses ranged from 2,400-6,000 micrograms/day administered by continuous infusion (100-250 micrograms/hour) or subcutaneously (1,500 micrograms three times a day). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatic steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis.

In children, the doses ranged from 50-3,000 microgram/day administered by continuous infusion (2.1-500 micrograms/hour) or subcutaneously (50-100 micrograms). The only adverse event reported was mild hyperglycaemia.

No unexpected adverse events have been reported in cancer patients receiving Sandostatin at doses of 3,000-30,000 micrograms/day in divided doses subcutaneously.

The management of overdosage is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatostatin and analogues, ATC code: H01CB02

Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits pathologically increased secretion of growth hormone (GH) and of peptides and serotonin produced within the GEP endocrine system.

In animals, octreotide is a more potent inhibitor of GH, glucagon and insulin release than somatostatin is, with greater selectivity for GH and glucagon suppression.

In healthy subjects Sandostatin has been shown to inhibit:
- release of GH stimulated by arginine, exercise- and insulin-induced hypoglycaemia,
- postprandial release of insulin, glucagon, gastrin, other peptides of the GEP endocrine system, and

arginine-stimulated release of insulin and glucagon,
- thyrotropin-releasing hormone (TRH)-stimulated release of thyroid-stimulating hormone (TSH).

Unlike somatostatin, octreotide inhibits GH secretion preferentially over insulin and its administration is not followed by rebound hypersecretion of hormones (i.e. GH in patients with acromegaly).

In acromegalic patients Sandostatin lowers plasma levels of GH and IGF-1. A GH reduction by 50% or more occurs in up to 90% patients, and a reduction of serum GH to <5 ng/mL can be achieved in about half of the cases. In most patients Sandostatin markedly reduces the clinical symptoms of the disease, such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia, paraesthesia. In patients with a large pituitary adenoma, Sandostatin treatment may result in some shrinkage of the tumour mass.

In patients with functional tumours of the GEP endocrine system, Sandostatin, because of its diverse endocrine effects, modifies a number of clinical features. Clinical improvement and symptomatic benefit occur in patients who still have symptoms related to their tumours despite previous therapies, which may include surgery, hepatic artery embolization, and various chemotherapies, e.g. streptozocin and 5-fluorouracil.

Sandostatin's effects in the different tumour types are as follows

Carcinoid tumours

Administration of Sandostatin may result in improvement of symptoms, particularly of flush and diarrhoea. In many cases, this is accompanied by a fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid.

VIPomas

The biochemical characteristic of these tumours is overproduction of vasoactive intestinal peptide (VIP). In most cases, administration of Sandostatin results in alleviation of the severe secretory diarrhoea typical of the condition, with consequent improvement in quality of life. This is accompanied by an improvement in associated electrolyte abnormalities, e.g. hypokalaemia, enabling enteral and parenteral fluid and electrolyte supplementation to be withdrawn. In some patients, computed tomography scanning suggests a slowing or arrest of progression of the tumour, or even tumour shrinkage, particularly of hepatic metastases. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas

Administration of Sandostatin results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of Sandostatin on the state of mild diabetes mellitus which frequently occurs is not marked and, in general, does not result in a reduction of requirements for insulin or oral hypoglycaemic agents. Sandostatin produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of Sandostatin often leads to an immediate reduction in plasma glucagon levels, this decrease is generally not maintained over a prolonged period of administration, despite continued symptomatic improvement.

Gastrinomas/Zollinger-Ellison syndrome

Therapy with proton pump inhibitors or H2 receptor blocking agents generally controls gastric acid hypersecretion. However, diarrhoea, which is also a prominent symptom, may not be adequately alleviated by proton pump inhibitors or H2 receptor blocking agents. Sandostatin can help to further reduce gastric acid hypersecretion and improve symptoms, including diarrhoea, as it provides suppression of elevated gastrin levels, in some patients.

Insulinomas

Administration of Sandostatin produces a fall in circulating immunoreactive insulin, which may, however, be of short duration (about 2 hours). In patients with operable tumours Sandostatin may help to restore and maintain normoglycaemia pre-operatively. In patients with inoperable benign or malignant tumours, glycaemic control may be improved without concomitant sustained reduction in circulating insulin levels.

Complications following pancreatic surgery

For patients undergoing pancreatic surgery, the peri- and post-operative administration of Sandostatin reduces the incidence of typical postoperative complications (e.g. pancreatic fistula, abscess and subsequent sepsis, postoperative acute pancreatitis).

Bleeding gastro-oesophageal varices

In patients presenting with bleeding gastro-oesophageal varices due to underlying cirrhosis, Sandostatin administration in combination with specific treatment (e.g. sclerotherapy) is associated with better control of bleeding and early re-bleeding, reduced transfusion requirements, and improved 5-day survival. While the precise mode of action of Sandostatin is not fully elucidated, it is postulated that Sandostatin reduces splanchnic blood flow through inhibition of vaso-active hormones (e.g. VIP, glucagon).

Treatment of TSH-secreting pituitary adenomas

The treatment effects of Sandostatin were prospectively observed in 21 patients and pooled with series of 37 published cases. Among 42 patients with evaluable biochemical data, there were 81% of patients (n=34) with satisfactory results (at least 50% reduction of TSH and substantial reduction of thyroid hormones), whereas 67% (n=28) had normalisations of TSH and thyroid hormones. In these patients, the response was maintained throughout the duration of treatment (up to 61 months, mean, 15.7 months).

Regarding clinical symptoms, a clear improvement was reported in 19 out of 32 patients with clinical hyperthyroidism. Tumour volume reduction greater than 20% was observed in 11 cases (41%) with a decrease greater than 50% in 4 cases (15%). The earliest reduction was reported after 14 days of treatment.

5.2 Pharmacokinetic properties

Absorption

After s.c. injection, Sandostatin is rapidly and completely absorbed. Peak plasma concentrations are reached within 30 minutes.

Distribution

The volume of distribution is 0.27 L/kg, and the total body clearance 160 mL/min. Plasma protein binding amounts to 65%. The amount of Sandostatin bound to blood cells is negligible.

Elimination

The elimination half-life after s.c. administration is 100 minutes. After i.v. injection, the elimination is biphasic, with half-lives of 10 and 90 minutes. Most of the peptide is eliminated via the faeces, while approximately 32% is excreted unchanged into the urine.

Special patient population

Impaired renal function did not affect the total exposure (AUC) to octreotide administered as s.c. injection.

The elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver

disease.

5.3 Preclinical safety data

Acute and repeated dose toxicology, genotoxicity, carcinogenicity and reproductive toxicology studies in animals revealed no specific safety concerns for humans.

Reproduction studies in animals revealed no evidence of teratogenic, embryo/foetal or other reproduction effects due to octreotide at parental doses of up to 1 mg/kg/day. Some retardation of physiological growth was noted in the offspring of rats which was transient and attributable to GH inhibition brought about by excessive pharmacodynamic activity (see section 4.6).

No specific studies were conducted in juvenile rats. In the pre- and post-natal developmental studies, reduced growth and maturation was observed in the F1 offspring of dams given octreotide during the entire pregnancy and lactation period. Delayed descent of the testes was observed for male F1 offsprings, but fertility of the affected F1 male pups remained normal. Thus, the abovementioned observations were transient and considered to be the consequence of GH inhibition.

Carcinogenicity/chronic toxicity

In rats receiving octreotide acetate at daily doses up to 1.25 mg/kg body weight, fibrosarcomas were observed, predominantly in a number of male animals, at the s.c. injection site after 52, 104 and 113/116 weeks. Local tumours also occurred in the control rats, however development of these tumours was attributed to disordered fibroplasia produced by sustained irritant effects at the injection sites, enhanced by the acidic lactic acid/mannitol vehicle. This non-specific tissue reaction appeared to be particular to rats. Neoplastic lesions were not observed either in mice receiving daily s.c. injections of octreotide at doses up to 2 mg/kg for 98 weeks, or in dogs treated with daily s.c. doses of the drug for 52 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal <and other handling>

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

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

LABELLING

PARTICULARS TO APPEAR ON <THE OUTER PACKAGING> <AND> <THE IMMEDIATE PACKAGING>

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

SANDOSTATIN and associated names (see Annex I) 0.05 mg/1 ml ampoules, solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion)
SANDOSTATIN and associated names (see Annex I) 0.1 mg/1 ml ampoules, solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion)
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[See Annex I - To be completed nationally]

Octreotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

{(Invented) name strength pharmaceutical form}

[See Annex I - To be completed nationally]

Octreotide

SC/IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

6. OTHER

PACKAGE LEAFLET

Package leaflet: Information for the patient

SANDOSTATIN and associated names (see Annex I) 0.05 mg/1 mL ampoules, solution for injection (s.c.) or concentrate for solution for infusion (i.v. infusion)
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[See Annex I - To be completed nationally]

Octreotide

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sandostatin is and what it is used for

Sandostatin is a synthetic compound derived from somatostatin, a substance normally found in the human body which inhibits the effects of certain hormones such as growth hormone. The advantages of Sandostatin over somatostatin are that it is stronger and its effects last longer.

Sandostatin is used
- in **acromegaly**, a condition where the body produces too much growth hormone. Normally, growth hormone controls growth of tissues, organs, and bones. Too much growth hormone leads to an increase in the size of bones and tissues, especially in the hands and feet. Sandostatin markedly reduces the symptoms of acromegaly, which include headache, excessive perspiration, numbness of the hands and feet, tiredness, and joint pain.
- to relieve symptoms associated with some **tumours of the gastrointestinal tract** (e.g. carcinoid tumours, VIPomas, glucagonomas, gastrinomas, insulinomas). In these conditions, there is overproduction of some specific hormones and other related substances by the stomach, bowels, or pancreas. This overproduction upsets the natural hormonal balance of the body and results in a variety of symptoms, such as flushing, diarrhoea, low blood pressure, rash, and weight loss. Treatment with Sandostatin helps to control these symptoms.
- to prevent **complications following surgery of the pancreas gland**. Treatment with Sandostatin helps to lower the risk of complications (e.g. abscess in the abdomen, inflammation of the pancreas gland) after the surgery.
- to stop bleeding and to protect from **re-bleeding from ruptured gastro-oesophageal varices** in

patients suffering from cirrhosis (chronic liver disease). Treatment with Sandostatin helps to control bleeding and reduce transfusion requirements.

- to treat pituitary tumours that produce too much thyroid-stimulating hormone (TSH). Too much thyroid-stimulating hormone (TSH) leads to hyperthyroidism.
  Sandostatin is used to treat people with pituitary tumours that produce too much thyroid-stimulating hormone (TSH):
  - when other types of treatment (surgery or radiotherapy) are not suitable or have not worked;
  - after radiotherapy, to cover the interim period until the radiotherapy becomes fully effective.

2. What you need to know before you use Sandostatin

Do not use Sandostatin:
- if you are allergic to octreotide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor before using Sandostatin:

- if you know that you have gallstones now, or have had them in the past; tell your doctor, as prolonged use of Sandostatin may result in gallstone formation. Your doctor may wish to check your gallbladder periodically.

- if you have problems with your blood sugar levels, either too high (diabetes) or too low (hypoglycaemia). When Sandostatin is used to treat bleeding from gastro-oesophageal varices; monitoring of blood sugar level is mandatory.

- if you have a history of vitamin B12 deprivation your doctor may wish to check your vitamin B12 level periodically.

Test and checks

If you receive treatment with Sandostatin over a long period of time, your doctor may wish to check your thyroid function periodically.

Your doctor will check your liver function.

Children
There is little experience with the use of Sandostatin in children.

Other medicines and Sandostatin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You can generally continue taking other medicines while on Sandostatin. However, certain medicines, such as cimetidine, ciclosporin, bromocriptine, quinidine and terfenadine have been reported to be affected by Sandostatin.

If you are taking a medicine to control your blood pressure (e.g. a beta blocker or a calcium channel blocker) or an agent to control your fluid and electrolyte balance, your doctor may need to adjust the dosage.

If you are diabetic, your doctor may need to adjust your insulin dosage.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Sandostatin should only be used during pregnancy if clearly needed.

Women of child-bearing age should use an effective contraceptive method during treatment.

Do not breast-feed while using Sandostatin. It is not known whether Sandostatin passes into breast milk.

Driving and using machines
Sandostatin has no or negligible effects on the ability to drive and use machines. However, some of the side effects you may experience while using Sandostatin, such as headache and tiredness, may reduce your ability to drive and use machines safely.

3. How to use Sandostatin

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Depending on the condition being treated, Sandostatin is given by:
- subcutaneous (under the skin) injection or
- intravenous (into a vein) infusion.

If you have liver cirrhosis (chronic liver disease), your doctor may need to adjust your maintenance dose.

Your doctor or nurse will explain to you how to inject Sandostatin under the skin, but infusion into a vein must always be performed by a health care professional.

- **Subcutaneous injection**

The upper arms, thighs, and abdomen are good areas for subcutaneous injection.

Choose a new site for each subcutaneous injection so that you do not irritate a particular area. Patients who will be injecting themselves must receive precise instructions from the doctor or nurse.

If you store the medicine in the refrigerator, it is recommended that you allow it to reach room temperature before using it. This will reduce the risk of pain at the site of injection. You can warm it up in your hand but do not heat it.

A few people experience pain at the site of the subcutaneous injection. This pain usually only lasts a short time. If this happens to you, you can relieve this by gently rubbing the site of injection for a few seconds afterwards.

Before using a Sandostatin ampoule, check the solution for particles or a change of colour. Do not use it if you see anything unusual.

To prevent contamination the cap of the multidose vials should be punctured not more than 10 times.

If you use more Sandostatin than you should
No life-threatening reactions have been reported after overdose of Sandostatin.

The symptoms of overdose are: irregular heart beat, low blood pressure, cardiac arrest, reduced supply of oxygen to the brain, severe upper stomach pain, yellow skin and eyes, nausea, loss of appetite, diarrhoea, weakness, tiredness, lack of energy, weight loss, abdominal swelling, discomfort and high level of lactic acid in the blood.

If you think that an overdose has happened and you experience such symptoms, tell your doctor straight away.

If you forget to use Sandostatin
Administer one dose as soon as you remember, and then continue as usual. It will not do any harm if you miss a dose, but you could get some temporary re-appearance of symptoms until you get back on schedule.

Do not inject a double dose of Sandostatin to make up for forgotten individual doses.

If you stop using Sandostatin
If you interrupt your treatment with Sandostatin your symptoms may come back. Therefore, do not stop using Sandostatin unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious. Tell your doctor straight away if you get any of the following:

Very common (may affect more than 1 in 10 people):
- Gallstones, leading to sudden back pain.
- Too much sugar in the blood.

Common (may affect up to 1 in 10 people):
- Underactive thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight; tiredness, feeling cold, or swelling at the front of the neck.
- Changes in thyroid function tests.
- Inflammation of the gallbladder (cholecystitis); symptoms may include pain in the upper right abdomen, fever, nausea, yellowing of the skin and eyes (jaundice).
- Too little sugar in the blood.
- Impaired glucose tolerance.
- Slow heart beat.

Uncommon (may affect up to 1 in 100 people):
- Thirst, low urine output, dark urine, dry flushed skin.
- Fast heart beat.

Other serious side effects
- Hypersensitivity (allergic) reactions including skin rash.
- A type of an allergic reaction (anaphylaxis) which causes difficulty in breathing or dizziness.
- An inflammation of the pancreas gland (pancreatitis); symptoms may include sudden pain in the upper abdomen, nausea, vomiting, diarrhoea.
- Liver inflammation (hepatitis); symptoms may include yellowing of the skin and eyes (jaundice), nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine.
- Irregular heart beat.

Tell your doctor straight away if you notice any of the side effects above.

Other side effects:
Tell your doctor, pharmacist or nurse if you notice any of the side effects listed below. They are usually mild and tend to disappear as treatment progresses.

Very common (may affect more than 1 in 10 people):
- Diarrhoea.

- Abdominal pain.
- Nausea.
- Constipation.
- Flatulence (wind).
- Headache.
- Local pain at the injection site.

Common (may affect up to 1 in 10 people):
- Stomach discomfort after meal (dyspepsia).
- Vomiting.
- Feeling of fullness in the stomach.
- Fatty stools.
- Loose stools.
- Discolouration of faeces.
- Dizziness.
- Loss of appetite.
- Change in liver function tests.
- Hair loss.
- Shortness of breath.
- Weakness.

If you get any side effects, please tell your doctor, nurse or pharmacist.

A few people experience pain at the site of the subcutaneous injection. This pain usually only lasts a short time. If this happens to you, you can relieve this by gently rubbing the site of injection for a few seconds afterwards.

If you are administering Sandostatin by subcutaneous injection, it may help to reduce the risk of gastrointestinal side effects if you avoid eating meals around the time of injection. It is therefore recommended that you inject Sandostatin between meals or when you go to bed.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sandostatin

[To be completed nationally]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the <label> <carton> <bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.>

<Do not use this medicine if you notice {description of the visible signs of deterioration}.>

<Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.>

6. Contents of the pack and other information

What Sandostatin contains
- The active substance(s) is (are)…
- The other ingredient(s) <(excipient(s))> is (are)...
  [To be completed nationally]

What Sandostatin looks like and contents of the pack
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer
[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:
[See Annex I - To be completed nationally]

This leaflet was last revised in {MM/YYYY}.
[To be completed nationally]

The following information is intended for healthcare professionals only:

- **Intravenous infusion (for health-care professionals)**

Sandostatin (octreotide acetate) is physically and chemically stable for 24 hours in sterile physiological saline solutions or sterile solutions of dextrose (glucose) 5% in water. However, because Sandostatin can affect glucose homeostasis, it is recommended that physiological saline solutions be used rather than dextrose. The diluted solutions are physically and chemically stable for at least 24 hours below 25°C. From a microbiological point of view, the diluted solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the user and should be at 2 to 8°C. Before administration the solution has to be brought to room temperature again.

The total time between reconstitution, dilution with infusion media, storage in a refrigerator, and end of administration must not be longer than 24 hours.

When Sandostatin is to be administered as intravenous infusion, the contents of one 0.5 mg ampoule should normally be dissolved in 60 mL physiological saline, and the resulting solution should be infused by means of an infusion pump. This should be repeated as often as necessary until the prescribed duration of treatment is reached.

Before using a Sandostatin ampoule, check the solution for particles or a change of colour. Do not use it if you see anything unusual.

To prevent contamination the cap of the multidose vials should be punctured not more than 10 times.

How much Sandostatin to use

The dose of Sandostatin depends on the condition being treated.

- **Acromegaly**

Treatment is usually started at 0.05 to 0.1 mg every 8 or 12 hours by subcutaneous injection. It is then changed according to its effect and relief of symptoms (such as tiredness, sweating and headache). In most patients the optimal daily dose will be 0.1 mg 3 times/day. A maximum dose of 1.5 mg/day should not be exceeded.

- **Tumours of the gastrointestinal tract**

Treatment is usually started at 0.05 mg once or twice a day by subcutaneous injection. Depending on response and tolerability, the dosage can be gradually increased to 0.1 mg to 0.2 mg 3 times/day. In carcinoid tumours, therapy should be discontinued if there is no improvement after 1 week of treatment at the maximum tolerated dose.

- **Complications following pancreatic surgery**

The usual dosage is 0.1 mg 3 times/day by subcutaneous injection for 1 week, starting at least 1 hour before surgery.

- **Bleeding gastro-oesophageal varices**

The recommended dosage is 25 micrograms/hour for 5 days by continuous intravenous infusion. Monitoring of blood sugar level is necessary during treatment.

- **TSH-secreting pituitary adenomas**

The dosage most generally effective is 100 micrograms three times a day by subcutaneous injection. The dose can be adjusted according to the responses of TSH and thyroid hormones. At least 5 days of treatment will be needed to judge the efficacy.