

**OCTREOTIDE 50MICROGRAM/ML SOLUTION FOR
INJECTION (PL 24897/0001)
OCTREOTIDE 100MICROGRAM/ML SOLUTION FOR
INJECTION (PL 24897/0002)
OCTREOTIDE 500MICROGRAM/ML SOLUTION FOR
INJECTION (PL 24897/0003)
OCTREOTIDE 200MICROGRAM/ML SOLUTION FOR
INJECTION (PL 24897/0004)**

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LAY SUMMARY

On 8th May 2008, the MHRA granted Sun Pharmaceuticals UK Limited Marketing Authorisations (licences) for the medicinal products Octreotide 50, 100, 500 and 200microgram/ml Solution for Injection (PL 24897/0001-4). These are prescription-only medicines (POM) used for the relief from symptoms of caused by overproduction of substances that act on the body's hormonal systems, to reduce levels of growth hormone and improve symptoms caused by overproduction of growth hormone.

Octreotide solution for injection is a synthetic version of the natural hormone somatostatin.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Octreotide 50, 100, 500 and 200microgram/ml Solution for Injection outweigh the risks, hence Marketing Authorisations have been granted.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Octreotide 50, 100, 500 and 200microgram/ml Solution for Injection (PL 24897/0001-4) on 8th May 2008 to Sun Pharmaceuticals UK Limited.

The products are prescription-only medicines, submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products of Sandostatin ampoules 0.05mg/ml, ampoules 0.1mg/ml, ampoules 0.5mg/ml and multidose vials 0.2mg/ml (PL 00101/0212-4 and 300), which were originally licensed to Novartis Pharmaceuticals UK Ltd in April 1989.

The products contain the active ingredient octreotide acetate, a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a longer duration of action. It inhibits pathologically increased secretion of growth hormone and of peptides and serotonin produced with the gastroenteropancreatic endocrine (GEP) system.

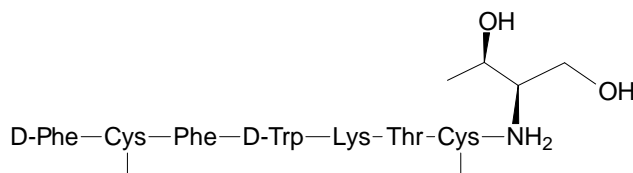
Octreotide 50, 100, 500 and 200microgram/ml Solution for Injection are indicated for:

- Relief of symptoms associated with functional gastroenteropancreatic endocrine tumours
- Symptomatic control and reduction of growth hormone and somatomedin c plasma levels in patients with acromegaly
- Prevention of complications following pancreatic surgery

PHARMACEUTICAL ASSESSMENT

INN: Octreotide
 Chemical name: D-Phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7)-disulfide

Structure:



Physical form: White to off white powder, with odour of acetic acid, freely soluble in water
 Molecular formula: C₄₉H₆₆N₁₀O₁₀S₂ (free peptide)
 Molecular weight: 1019.26 (free peptide)

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance octreotide acetate. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability studies, a suitable retest period has been proposed for the active substance. Suitable post approval stability commitments have been given to provide additional stability data as and when it becomes available.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium acetate trihydrate, glacial acetic acid, sodium chloride and water for injections. The 200microgram/ml strength also contains phenol.

All excipients used comply with their respective Ph Eur monograph.

None of the excipients used contain materials of animal or human origin.

Product development

The objective of the development programme was to produce solutions containing octreotide that were safe and could be considered as generic medicinal products to

Sandostatin ampoules 0.05mg/ml, ampoules 0.1mg/ml, ampoules 0.5mg/ml and multidose vials 0.2mg/ml.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength of product. The results appear satisfactory.

Finished product specification

The finished product specifications are satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificate of analysis have been provided for all working standards used.

Container-closure system

The 50, 100 and 500 microgram/ml strengths are packaged in 1ml colourless ampoules and the 200 microgram/ml strength is packaged in 5ml colourless type I glass vials, with rubber stopper and aluminium seal.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding contact with solutions for injection.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set for all strengths, with the storage instructions "For prolonged storage, vials should be stored between 2°C and 8°C. For day-to-day use they may be stored at room temperature for up to two weeks. Protect from light. Do not freeze".

Bioequivalence

See Clinical Assessment.

ADMINISTRATIVE

Expert Report

A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)

These are consistent with those for the reference products and are satisfactory.

Labelling

These are satisfactory

Patient Information Leaflet

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Forms

These are satisfactory.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance used in the proposed and reference products.

PRECLINICAL ASSESSMENT

This application is for generic medicinal products of Sandostatin ampoules 0.05mg/ml, ampoules 0.1mg/ml, ampoules 0.5mg/ml and multidose vials 0.2mg/ml (Novartis Pharmaceuticals UK Limited), which have been licensed within the EU for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INDICATIONS

The indications are consistent with those for the reference products and are satisfactory.

2. DOSE & DOSE SCHEDULE

The dose and dosage schedule are consistent with those for the reference products and are satisfactory.

3. CLINICAL PHARMACOLOGY

The clinical (and preclinical) expert reports provide an adequate review of the known pharmacodynamics and pharmacokinetics of octreotide acetate. No reference is made to any new data that would have affected the products under consideration.

4. EFFICACY

The clinical expert report provides an adequate review of the efficacy of octreotide acetate for the listed indications.

5. SAFETY

The clinical expert report provides an adequate review of the clinical safety of octreotide acetate. The toxicity from octreotide acetate is described in detail per organ system. No reference is made to any new data that would have affected the marketing authorisation for the products under consideration.

6. EXPERT REPORTS

The expert reports are written by appropriately qualified experts.

7. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are consistent with the reference products and are satisfactory.

8. PATIENT INFORMATION LEAFLET (PIL)

This is consistent with that for the reference products and is satisfactory.

9. LABELLING

Full colour mock-ups are provided and are satisfactory.

10. MEDICAL CONCLUSION

Marketing authorisations may be granted for these products.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Octreotide 50, 100, 500 and 200microgram/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

As the products are solutions for injection, containing identical excipients to those of the brand leaders, no bioequivalence data were required and the proposed products are considered to be generic medicinal products of the brand leader products.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with octreotide acetate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 13 th February 2006
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 20 th February 2006
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 11 th August 2006, and further information relating to the quality dossiers on 7 th June 2006, 2 nd August 2007 and 6 th August 2007
4	The applicant responded to the MHRA's requests, providing further information on 17 th August 2006 for the clinical sections, and on 2 nd August 2007, 6 th August 2007 and 19 th March 2008 for the quality sections.
5	The applications were determined on 8 th May 2008

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Octreotide 50 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule contains octreotide acetate equivalent to 50 micrograms of octreotide.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

1ml ampoule containing clear colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GEP tumours

For the relief of symptoms associated with functional gastroenteropancreatic endocrine tumours including:

- carcinoid tumours with features of carcinoid syndrome
- VIPomas
- glucagonomas

Octreotide is not antitumour therapy and is not curative in these patients.

Acromegaly

For symptomatic control and reduction of growth hormone and somatomedin c plasma levels in patients with acromegaly:

- in short term treatment, prior to pituitary surgery, or
- in long term treatment in those who are inadequately controlled by pituitary surgery, radiotherapy, or in the interim period until radiotherapy becomes effective.

Octreotide is indicated for acromegalic patients for whom surgery is inappropriate.

Evidence from short term studies demonstrate that tumour size is reduced in some patients (prior to surgery); further tumour shrinkage however cannot be expected as a feature of continued long term treatment.

Prevention of complications following pancreatic surgery

Route of administration

Subcutaneous or intravenous use.

4.2 Posology and method of administration

GEP tumours

Initially 0.05 mg once or twice daily by s.c. injection. Depending on response, dosage can be gradually increased to 0.2 mg three times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses are variable.

The recommended route of administration is subcutaneous, however, in instances where a rapid response is required, e.g. carcinoid crises, the initial recommended dose of octreotide may be administered by the intravenous route, diluted and given as a bolus, whilst monitoring the cardiac rhythm.

In carcinoid tumours, if there is no beneficial effect within a week, continued therapy is not recommended.

Acromegaly

0.1 – 0.2 mg three times daily by s.c. injection. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH less than 2.5ng/ml, 5mU/l; IGF-1 within normal range) and clinical symptoms, and on tolerability. For patients on a stable dose

of octreotide, assessment of GH should be made every 12 months. Six-monthly monitoring may be necessary in those patients whose clinical and biochemical control is less adequate.

If no relevant reduction of growth hormone levels and no improvement of clinical symptoms have been achieved within three months of starting treatment, therapy should be discontinued.

For the prevention of complications following pancreatic surgery

0.1 mg three times daily by subcutaneous injection for 7 consecutive days, starting on the day of operation at least one hour before laparotomy.

Use in patients with impaired renal function

Impaired renal function did not affect the total exposure (AUC; area under the curve) to octreotide when administered s.c. therefore, no dose adjustment of octreotide is necessary.

Use in patients with impaired hepatic function

In a study with octreotide administered s.c. and i.v. it was shown that the elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease. In patients with liver cirrhosis, an adjustment of the maintenance dose may therefore be necessary.

Use in the elderly

In elderly patients treated with octreotide, there is no evidence for reduced tolerability or altered dosage requirements.

Use in children

Experience with octreotide in children is very limited.

4.3 Contraindications

Known hypersensitivity to octreotide or to any component of the formulations (see 6.1 List of excipients).

4.4 Special warnings and precautions for use

As growth hormone 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.

Sudden escape of gastroenteropancreatic endocrine tumours from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Octreotide may increase the depth and duration of hypoglycaemia in patients with insulinoma. This is because it is relatively more potent in inhibiting growth hormone and glucagon secretion than in inhibiting insulin and because its duration of insulin inhibition is shorter. If octreotide is given to a patient with insulinoma, close monitoring is necessary on introduction of therapy and at each change of dosage. Marked fluctuations of blood glucose may be reduced by more frequent administration of octreotide.

Octreotide may reduce insulin or oral hypoglycaemic requirements in patients with type I diabetes mellitus. In non-diabetics and type II diabetics with particularly intact insulin reserves, octreotide administration can result in prandial increases in glycaemia.

Thyroid function should be monitored in patients receiving long-term octreotide therapy.

Octreotide exerts an inhibiting effect on gallbladder motility, bile acid secretion and bile flow and there is an acknowledged association with the development of gallstones. The incidence of gallstone formation with octreotide treatment is estimated to be between 15 - 30 %.

Ultrasonic examination of the gallbladder, before and at about 6 to 12 month intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated in the normal manner with due attention to abrupt withdrawal of the drug.

In patients with cirrhosis, dosage adjustment may be necessary (see Section 4.2 Posology and Method of Administration).

4.5 Interaction with other medicinal products and other forms of interaction

Octreotide has been reported to reduce the intestinal absorption of cyclosporin and to delay that of cimetidine.

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

Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that 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. carbamazepine, digoxin, warfarin and terfenadine).

4.6 Pregnancy and lactation

Experience with octreotide in pregnant or nursing women is very limited, and they should therefore be given the drug only under compelling circumstances.

Women receiving treatment with octreotide should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No data exists on the effects of octreotide on the ability to drive and use machines.

4.8 Undesirable effects

The main side-effects are local and gastrointestinal.

Body as a whole

Rare: hypersensitivity skin reactions; hair loss and isolated reports of anaphylactic reactions have been observed.

Cardiovascular system

Isolated cases of bradycardia.

Gastrointestinal system

Anorexia, nausea, vomiting, abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea and steatorrhea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side-effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side-effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Hepatobiliary

Prolonged use of octreotide may result in gallstone formation (see 4.4 Special warnings and precautions for use), and there have been isolated cases of biliary colic following the abrupt withdrawal of the drug in acromegalic patients in whom biliary sludge or gallstones had developed.

There have been isolated reports of hepatic dysfunctions associated with octreotide administration. These consist of:

- acute hepatitis, without cholestasis, where transaminase values have normalised on withdrawal of octreotide, or
- slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma-glutamyl transferase and, to a lesser extent, transaminases.

Pancreas

Because of its inhibitory action on growth hormone, glucagon, and insulin release, octreotide may affect glucose regulation. Postprandial 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 observed within the first hours or days of octreotide treatment and resolves on withdrawal of the drug. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term octreotide treatment.

Local 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.

4.9 Overdose

Doses of up to 2000 microgrammes octreotide given as subcutaneous tid for several months have been well tolerated.

No life-threatening reactions have been reported after acute overdosage. The maximum single dose given to an adult so far has been 1 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved in 24 hours of drug administration.

One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (250 microgrammes per hour for forty eight hours instead of 25 microgrammes per hour). He experienced no side-effects.

The management of overdosage is symptomatic.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antigrowth hormones (ATC code H01B C02).

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

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

In normal healthy subjects octreotide, like somatostatin, has been shown to inhibit

- release of growth hormone stimulated by arginine, exercise and insulin-induced hypoglycaemia

- postprandial release of insulin, glucagon, gastrin other peptides of the gastroenteropancreatic system; arginine-stimulated release of insulin and glucagon and

- thyrotropin-releasing hormone (TRH) - stimulated release of thyroid stimulating hormone (TSH).

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

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

In patients with acromegaly, octreotide consistently lowers GH and normalises IGF-1 serum concentrations in the majority of patients. In most patients, octreotide markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue,

osteoarthralgia and carpal tunnel syndrome. In individual patients with GH-secreting pituitary adenoma, octreotide was reported to lead to shrinkage of the tumour mass.

For patients with functional tumours of the gastroenteropancreatic endocrine system, treatment with octreotide provides continuous control of symptoms related to the underlying disease. The effects of octreotide in different types of gastroenteropancreatic tumours are as follows:

Carcinoid tumours

Administration of octreotide may result in improvement of symptoms, particularly of flushing and diarrhoea. In many cases, this is accompanied by a falling 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 octreotide 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. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas

Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of octreotide 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. Octreotide produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of octreotide 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.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, octreotide 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 octreotide bound to blood cells is negligible.

Elimination

The elimination half-life after subcutaneous administrations is 100 minutes. After intravenous injection the elimination is biphasic with half-lives of 10 and 90 minutes respectively. About 32 % is excreted unchanged into the urine.

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Studies in animals showed transient growth retardation of offspring, possibly consequent upon the specific endocrine profiles of the species tested, but there was no evidence of foetotoxic, teratogenic, or other reproduction effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Glacial acetic acid
Sodium chloride
Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

For prolonged storage, ampoules should be stored between 2°C and 8°C. For day-to-day use they may be stored at room temperature for up to two weeks. Protect from light. Do not freeze.

6.5 Nature and contents of container

1 ml ampoule of uncoloured glass containing clear colourless solution.
Boxes of 5 ampoules.

6.6 Special precautions for disposal

For i.v. use octreotide should be diluted with normal saline to a ratio of not less than 1 vol : 1 vol and not more than 1 vol : 9 vol . Dilution of octreotide with glucose solution is not recommended.

If octreotide has been diluted, the prepared solution may be kept at room temperature but should be administered within 8 hours of preparation.

To reduce local discomfort, let the solution reach room temperature before injection. Avoid multiple injections at short intervals at the same site.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceuticals UK Limited
4/5 Loveridge Mews,
London NW6 2DP
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 24897/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/05/2008

10 DATE OF REVISION OF THE TEXT

12/05/2008

11 DOSIMETRY (IF APPLICABLE)**12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

1 NAME OF THE MEDICINAL PRODUCT

Octreotide 100 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule contains octreotide acetate equivalent to 100 micrograms of octreotide.
For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

1ml ampoule containing clear colourless solution for injection.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications****GEP tumours**

For the relief of symptoms associated with functional gastroenteropancreatic endocrine tumours including:

- carcinoid tumours with features of carcinoid syndrome
- VIPomas
- glucagonomas

Octreotide is not antitumour therapy and is not curative in these patients.

Acromegaly

For symptomatic control and reduction of growth hormone and somatomedin c plasma levels in patients with acromegaly:

- in short term treatment, prior to pituitary surgery, or
- in long term treatment in those who are inadequately controlled by pituitary surgery, radiotherapy, or in the interim period until radiotherapy becomes effective.

Octreotide is indicated for acromegalic patients for whom surgery is inappropriate.

Evidence from short term studies demonstrate that tumour size is reduced in some patients (prior to surgery); further tumour shrinkage however cannot be expected as a feature of continued long term treatment.

Prevention of complications following pancreatic surgery**Route of administration**

Subcutaneous or intravenous use.

4.2 Posology and method of administration**GEP tumours**

Initially 0.05 mg once or twice daily by s.c. injection. Depending on response, dosage can be gradually increased to 0.2 mg three times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses are variable.

The recommended route of administration is subcutaneous, however, in instances where a rapid response is required, e.g. carcinoid crises, the initial recommended dose of octreotide may be administered by the intravenous route, diluted and given as a bolus, whilst monitoring the cardiac rhythm.

In carcinoid tumours, if there is no beneficial effect within a week, continued therapy is not recommended.

Acromegaly

0.1 – 0.2 mg three times daily by s.c. injection. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH less than 2.5ng/ml, 5mU/l; IGF-1 within normal range) and clinical symptoms, and on tolerability. For patients on a stable dose of octreotide, assessment of GH should be made every 12 months. Six-monthly monitoring may be necessary in those patients whose clinical and biochemical control is less adequate.

If no relevant reduction of growth hormone levels and no improvement of clinical symptoms have been achieved within three months of starting treatment, therapy should be discontinued.

For the prevention of complications following pancreatic surgery

0.1 mg three times daily by subcutaneous injection for 7 consecutive days, starting on the day of operation at least one hour before laparotomy.

Use in patients with impaired renal function

Impaired renal function did not affect the total exposure (AUC; area under the curve) to octreotide when administered s.c. therefore, no dose adjustment of octreotide is necessary.

Use in patients with impaired hepatic function

In a study with octreotide administered s.c. and i.v. it was shown that the elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease. In patients with liver cirrhosis, an adjustment of the maintenance dose may therefore be necessary.

Use in the elderly

In elderly patients treated with octreotide, there is no evidence for reduced tolerability or altered dosage requirements.

Use in children

Experience with octreotide in children is very limited.

4.3 Contraindications

Known hypersensitivity to octreotide or to any component of the formulations (see 6.1 List of excipients).

4.4 Special warnings and precautions for use

As growth hormone 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.

Sudden escape of gastroenteropancreatic endocrine tumours from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Octreotide may increase the depth and duration of hypoglycaemia in patients with insulinoma. This is because it is relatively more potent in inhibiting growth hormone and glucagon secretion than in inhibiting insulin and because its duration of insulin inhibition is shorter. If octreotide is given to a patient with insulinoma, close monitoring is necessary on introduction of therapy and at each change of dosage. Marked fluctuations of blood glucose may be reduced by more frequent administration of octreotide.

Octreotide may reduce insulin or oral hypoglycaemic requirements in patients with type I diabetes mellitus. In non-diabetics and type II diabetics with particularly intact insulin reserves, octreotide administration can result in prandial increases in glycaemia.

Thyroid function should be monitored in patients receiving long-term octreotide therapy.

Octreotide exerts an inhibiting effect on gallbladder motility, bile acid secretion and bile flow and there is an acknowledged association with the development of gallstones. The incidence of gallstone formation with octreotide treatment is estimated to be between 15 - 30 %.

Ultrasonic examination of the gallbladder, before and at about 6 to 12 month intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated in the normal manner with due attention to abrupt withdrawal of the drug.

In patients with cirrhosis, dosage adjustment may be necessary (see Section 4.2 Posology and Method of Administration).

4.5 Interaction with other medicinal products and other forms of interaction

Octreotide has been reported to reduce the intestinal absorption of cyclosporin and to delay that of cimetidine.

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

Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that 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. carbamazepine, digoxin, warfarin and terfenadine).

4.6 Pregnancy and lactation

Experience with octreotide in pregnant or nursing women is very limited, and they should therefore be given the drug only under compelling circumstances.

Women receiving treatment with octreotide should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No data exists on the effects of octreotide on the ability to drive and use machines.

4.8 Undesirable effects

The main side-effects are local and gastrointestinal.

Body as a whole

Rare: hypersensitivity skin reactions; hair loss and isolated reports of anaphylactic reactions have been observed.

Cardiovascular system

Isolated cases of bradycardia.

Gastrointestinal system

Anorexia, nausea, vomiting, abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea and steatorrhea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side-effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side-effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Hepatobiliary

Prolonged use of octreotide may result in gallstone formation (see 4.4 Special warnings and precautions for use), and there have been isolated cases of biliary colic following the abrupt withdrawal of the drug in acromegalic patients in whom biliary sludge or gallstones had developed.

There have been isolated reports of hepatic dysfunctions associated with octreotide administration. These consist of:

- acute hepatitis, without cholestasis, where transaminase values have normalised on withdrawal of octreotide, or
- slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma-glutamyl transferase and, to a lesser extent, transaminases.

Pancreas

Because of its inhibitory action on growth hormone, glucagon, and insulin release, octreotide may affect glucose regulation. Postprandial 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 observed within the first hours or days of octreotide treatment and resolves on withdrawal of the drug. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term octreotide treatment.

Local 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.

4.9 Overdose

Doses of up to 2000 microgrammes octreotide given as subcutaneous tid for several months have been well tolerated.

No life-threatening reactions have been reported after acute overdosage. The maximum single dose given to an adult so far has been 1 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved in 24 hours of drug administration.

One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (250 microgrammes per hour for forty eight hours instead of 25 microgrammes per hour). He experienced no side-effects.

The management of overdosage is symptomatic.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antigrowth hormones (ATC code H01B C02).

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

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

In normal healthy subjects octreotide, like somatostatin, has been shown to inhibit

- release of growth hormone stimulated by arginine, exercise and insulin-induced hypoglycaemia

- postprandial release of insulin, glucagon, gastrin other peptides of the gastroenteropancreatic system; arginine-stimulated release of insulin and glucagon and

- thyrotropin-releasing hormone (TRH) - stimulated release of thyroid stimulating hormone (TSH).

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

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

In patients with acromegaly, octreotide consistently lowers GH and normalises IGF-1 serum concentrations in the majority of patients. In most patients, octreotide markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue,

osteoarthralgia and carpal tunnel syndrome. In individual patients with GH-secreting pituitary adenoma, octreotide was reported to lead to shrinkage of the tumour mass.

For patients with functional tumours of the gastroenteropancreatic endocrine system, treatment with octreotide provides continuous control of symptoms related to the underlying disease. The effects of octreotide in different types of gastroenteropancreatic tumours are as follows:

Carcinoid tumours

Administration of octreotide may result in improvement of symptoms, particularly of flushing and diarrhoea. In many cases, this is accompanied by a falling 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 octreotide 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. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas

Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of octreotide 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. Octreotide produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of octreotide 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.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, octreotide 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 octreotide bound to blood cells is negligible.

Elimination

The elimination half-life after subcutaneous administrations is 100 minutes. After intravenous injection the elimination is biphasic with half-lives of 10 and 90 minutes respectively. About 32 % is excreted unchanged into the urine.

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Studies in animals showed transient growth retardation of offspring, possibly consequent upon the specific endocrine profiles of the species tested, but there was no evidence of foetotoxic, teratogenic, or other reproduction effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Glacial acetic acid
Sodium chloride
Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

For prolonged storage, ampoules should be stored between 2°C and 8°C. For day-to-day use they may be stored at room temperature for up to two weeks. Protect from light. Do not freeze.

6.5 Nature and contents of container

1 ml ampoule of uncoloured glass containing clear colourless solution.
Boxes of 5 ampoules.

6.6 Special precautions for disposal

For i.v. use octreotide should be diluted with normal saline to a ratio of not less than 1 vol : 1 vol and not more than 1 vol : 9 vol . Dilution of octreotide with glucose solution is not recommended.

If octreotide has been diluted, the prepared solution may be kept at room temperature but should be administered within 8 hours of preparation.

To reduce local discomfort, let the solution reach room temperature before injection. Avoid multiple injections at short intervals at the same site.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceuticals UK Limited
4/5 Loveridge Mews,
London NW6 2DP
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 24897/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/05/2008

10 DATE OF REVISION OF THE TEXT

12/05/2008

11 DOSIMETRY (IF APPLICABLE)**12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

1 NAME OF THE MEDICINAL PRODUCT

Octreotide 500 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule contains octreotide acetate equivalent to 500 micrograms of octreotide.
For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

1ml ampoule containing clear colourless solution for injection.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications****GEP tumours**

For the relief of symptoms associated with functional gastroenteropancreatic endocrine tumours including:

- carcinoid tumours with features of carcinoid syndrome
- VIPomas
- glucagonomas

Octreotide is not antitumour therapy and is not curative in these patients.

Acromegaly

For symptomatic control and reduction of growth hormone and somatomedin c plasma levels in patients with acromegaly:

- in short term treatment, prior to pituitary surgery, or
- in long term treatment in those who are inadequately controlled by pituitary surgery, radiotherapy, or in the interim period until radiotherapy becomes effective.

Octreotide is indicated for acromegalic patients for whom surgery is inappropriate.

Evidence from short term studies demonstrate that tumour size is reduced in some patients (prior to surgery); further tumour shrinkage however cannot be expected as a feature of continued long term treatment.

Prevention of complications following pancreatic surgery**Route of administration**

Subcutaneous or intravenous use.

4.2 Posology and method of administration**GEP tumours**

Initially 0.05 mg once or twice daily by s.c. injection. Depending on response, dosage can be gradually increased to 0.2 mg three times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses are variable.

The recommended route of administration is subcutaneous, however, in instances where a rapid response is required, e.g. carcinoid crises, the initial recommended dose of octreotide may be administered by the intravenous route, diluted and given as a bolus, whilst monitoring the cardiac rhythm.

In carcinoid tumours, if there is no beneficial effect within a week, continued therapy is not recommended.

Acromegaly

0.1 – 0.2 mg three times daily by s.c. injection. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH less than 2.5ng/ml, 5mU/l; IGF-1 within normal range) and clinical symptoms, and on tolerability. For patients on a stable dose of octreotide, assessment of GH should be made every 12 months. Six-monthly monitoring may be necessary in those patients whose clinical and biochemical control is less adequate.

If no relevant reduction of growth hormone levels and no improvement of clinical symptoms have been achieved within three months of starting treatment, therapy should be discontinued.

For the prevention of complications following pancreatic surgery

0.1 mg three times daily by subcutaneous injection for 7 consecutive days, starting on the day of operation at least one hour before laparotomy.

Use in patients with impaired renal function

Impaired renal function did not affect the total exposure (AUC; area under the curve) to octreotide when administered s.c. therefore, no dose adjustment of octreotide is necessary.

Use in patients with impaired hepatic function

In a study with octreotide administered s.c. and i.v. it was shown that the elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease. In patients with liver cirrhosis, an adjustment of the maintenance dose may therefore be necessary.

Use in the elderly

In elderly patients treated with octreotide, there is no evidence for reduced tolerability or altered dosage requirements.

Use in children

Experience with octreotide in children is very limited.

4.3 Contraindications

Known hypersensitivity to octreotide or to any component of the formulations (see 6.1 List of excipients).

4.4 Special warnings and precautions for use

As growth hormone 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.

Sudden escape of gastroenteropancreatic endocrine tumours from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Octreotide may increase the depth and duration of hypoglycaemia in patients with insulinoma. This is because it is relatively more potent in inhibiting growth hormone and glucagon secretion than in inhibiting insulin and because its duration of insulin inhibition is shorter. If octreotide is given to a patient with insulinoma, close monitoring is necessary on introduction of therapy and at each change of dosage. Marked fluctuations of blood glucose may be reduced by more frequent administration of octreotide.

Octreotide may reduce insulin or oral hypoglycaemic requirements in patients with type I diabetes mellitus. In non-diabetics and type II diabetics with particularly intact insulin reserves, octreotide administration can result in prandial increases in glycaemia.

Thyroid function should be monitored in patients receiving long-term octreotide therapy.

Octreotide exerts an inhibiting effect on gallbladder motility, bile acid secretion and bile flow and there is an acknowledged association with the development of gallstones. The incidence of gallstone formation with octreotide treatment is estimated to be between 15 - 30 %.

Ultrasonic examination of the gallbladder, before and at about 6 to 12 month intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated in the normal manner with due attention to abrupt withdrawal of the drug.

In patients with cirrhosis, dosage adjustment may be necessary (see Section 4.2 Posology and Method of Administration).

4.5 Interaction with other medicinal products and other forms of interaction

Octreotide has been reported to reduce the intestinal absorption of cyclosporin and to delay that of cimetidine.

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

Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that 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. carbamazepine, digoxin, warfarin and terfenadine).

4.6 Pregnancy and lactation

Experience with octreotide in pregnant or nursing women is very limited, and they should therefore be given the drug only under compelling circumstances.

Women receiving treatment with octreotide should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No data exists on the effects of octreotide on the ability to drive and use machines.

4.8 Undesirable effects

The main side-effects are local and gastrointestinal.

Body as a whole

Rare: hypersensitivity skin reactions; hair loss and isolated reports of anaphylactic reactions have been observed.

Cardiovascular system

Isolated cases of bradycardia.

Gastrointestinal system

Anorexia, nausea, vomiting, abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea and steatorrhea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side-effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side-effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Hepatobiliary

Prolonged use of octreotide may result in gallstone formation (see 4.4 Special warnings and precautions for use), and there have been isolated cases of biliary colic following the abrupt withdrawal of the drug in acromegalic patients in whom biliary sludge or gallstones had developed.

There have been isolated reports of hepatic dysfunctions associated with octreotide administration. These consist of:

- acute hepatitis, without cholestasis, where transaminase values have normalised on withdrawal of octreotide, or
- slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma-glutamyl transferase and, to a lesser extent, transaminases.

Pancreas

Because of its inhibitory action on growth hormone, glucagon, and insulin release, octreotide may affect glucose regulation. Postprandial 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 observed within the first hours or days of octreotide treatment and resolves on withdrawal of the drug. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term octreotide treatment.

Local 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.

4.9 Overdose

Doses of up to 2000 microgrammes octreotide given as subcutaneous tid for several months have been well tolerated.

No life-threatening reactions have been reported after acute overdosage. The maximum single dose given to an adult so far has been 1 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved in 24 hours of drug administration.

One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (250 microgrammes per hour for forty eight hours instead of 25 microgrammes per hour). He experienced no side-effects.

The management of overdosage is symptomatic.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antigrowth hormones (ATC code H01B C02).

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

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

In normal healthy subjects octreotide, like somatostatin, has been shown to inhibit

- release of growth hormone stimulated by arginine, exercise and insulin-induced hypoglycaemia

- postprandial release of insulin, glucagon, gastrin other peptides of the gastroenteropancreatic system; arginine-stimulated release of insulin and glucagon and

- thyrotropin-releasing hormone (TRH) - stimulated release of thyroid stimulating hormone (TSH).

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

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

In patients with acromegaly, octreotide consistently lowers GH and normalises IGF-1 serum concentrations in the majority of patients. In most patients, octreotide markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue,

osteoarthralgia and carpal tunnel syndrome. In individual patients with GH-secreting pituitary adenoma, octreotide was reported to lead to shrinkage of the tumour mass.

For patients with functional tumours of the gastroenteropancreatic endocrine system, treatment with octreotide provides continuous control of symptoms related to the underlying disease. The effects of octreotide in different types of gastroenteropancreatic tumours are as follows:

Carcinoid tumours

Administration of octreotide may result in improvement of symptoms, particularly of flushing and diarrhoea. In many cases, this is accompanied by a falling 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 octreotide 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. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas

Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of octreotide 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. Octreotide produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of octreotide 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.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, octreotide 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 octreotide bound to blood cells is negligible.

Elimination

The elimination half-life after subcutaneous administrations is 100 minutes. After intravenous injection the elimination is biphasic with half-lives of 10 and 90 minutes respectively. About 32 % is excreted unchanged into the urine.

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Studies in animals showed transient growth retardation of offspring, possibly consequent upon the specific endocrine profiles of the species tested, but there was no evidence of foetotoxic, teratogenic, or other reproduction effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Glacial acetic acid
Sodium chloride
Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

For prolonged storage, ampoules should be stored between 2°C and 8°C. For day-to-day use they may be stored at room temperature for up to two weeks. Protect from light. Do not freeze.

6.5 Nature and contents of container

1 ml ampoule of uncoloured glass containing clear colourless solution.
Boxes of 5 ampoules.

6.6 Special precautions for disposal

For i.v. use octreotide should be diluted with normal saline to a ratio of not less than 1 vol : 1 vol and not more than 1 vol : 9 vol . Dilution of octreotide with glucose solution is not recommended.

If octreotide has been diluted, the prepared solution may be kept at room temperature but should be administered within 8 hours of preparation.

To reduce local discomfort, let the solution reach room temperature before injection. Avoid multiple injections at short intervals at the same site.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceuticals UK Limited
4/5 Loveridge Mews,
London NW6 2DP
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 24897/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/05/2008

10 DATE OF REVISION OF THE TEXT

12/05/2008

11 DOSIMETRY (IF APPLICABLE)**12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

1 NAME OF THE MEDICINAL PRODUCT

Octreotide 200 micrograms/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One multidose vial contains octreotide acetate equivalent to 1000 micrograms of octreotide in 5 ml.

For full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

5ml ampoule containing clear colourless solution for injection.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications****GEP tumours**

For the relief of symptoms associated with functional gastroenteropancreatic endocrine tumours including:

- carcinoid tumours with features of carcinoid syndrome
- VIPomas
- glucagonomas

Octreotide is not antitumour therapy and is not curative in these patients.

Acromegaly

For symptomatic control and reduction of growth hormone and somatomedin c plasma levels in patients with acromegaly:

- in short term treatment, prior to pituitary surgery, or
- in long term treatment in those who are inadequately controlled by pituitary surgery, radiotherapy, or in the interim period until radiotherapy becomes effective.

Octreotide is indicated for acromegalic patients for whom surgery is inappropriate.

Evidence from short term studies demonstrate that tumour size is reduced in some patients (prior to surgery); further tumour shrinkage however cannot be expected as a feature of continued long term treatment.

Prevention of complications following pancreatic surgery**Route of administration**

Subcutaneous or intravenous use.

4.2 Posology and method of administration**GEP tumours**

Initially 0.05 mg once or twice daily by s.c. injection. Depending on response, dosage can be gradually increased to 0.2 mg three times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses are variable.

The recommended route of administration is subcutaneous, however, in instances where a rapid response is required, e.g. carcinoid crises, the initial recommended dose of octreotide may be administered by the intravenous route, diluted and given as a bolus, whilst monitoring the cardiac rhythm.

In carcinoid tumours, if there is no beneficial effect within a week, continued therapy is not recommended.

Acromegaly

0.1 – 0.2 mg three times daily by s.c. injection. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH less than 2.5ng/ml, 5mU/l; IGF-1 within normal range) and clinical symptoms, and on tolerability. For patients on a stable dose

of octreotide, assessment of GH should be made every 12 months. Six-monthly monitoring may be necessary in those patients whose clinical and biochemical control is less adequate.

If no relevant reduction of growth hormone levels and no improvement of clinical symptoms have been achieved within three months of starting treatment, therapy should be discontinued.

For the prevention of complications following pancreatic surgery

0.1 mg three times daily by subcutaneous injection for 7 consecutive days, starting on the day of operation at least one hour before laparotomy.

Use in patients with impaired renal function

Impaired renal function did not affect the total exposure (AUC; area under the curve) to octreotide when administered s.c. therefore, no dose adjustment of octreotide is necessary.

Use in patients with impaired hepatic function

In a study with octreotide administered s.c. and i.v. it was shown that the elimination capacity may be reduced in patients with liver cirrhosis, but not in patients with fatty liver disease. In patients with liver cirrhosis, an adjustment of the maintenance dose may therefore be necessary.

Use in the elderly

In elderly patients treated with octreotide, there is no evidence for reduced tolerability or altered dosage requirements.

Use in children

Experience with octreotide in children is very limited.

4.3 Contraindications

Known hypersensitivity to octreotide or to any component of the formulations (see 6.1 List of excipients).

4.4 Special warnings and precautions for use

As growth hormone 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.

Sudden escape of gastroenteropancreatic endocrine tumours from symptomatic control by octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Octreotide may increase the depth and duration of hypoglycaemia in patients with insulinoma. This is because it is relatively more potent in inhibiting growth hormone and glucagon secretion than in inhibiting insulin and because its duration of insulin inhibition is shorter. If octreotide is given to a patient with insulinoma, close monitoring is necessary on introduction of therapy and at each change of dosage. Marked fluctuations of blood glucose may be reduced by more frequent administration of octreotide.

Octreotide may reduce insulin or oral hypoglycaemic requirements in patients with type I diabetes mellitus. In non-diabetics and type II diabetics with particularly intact insulin reserves, octreotide administration can result in prandial increases in glycaemia.

Thyroid function should be monitored in patients receiving long-term octreotide therapy.

Octreotide exerts an inhibiting effect on gallbladder motility, bile acid secretion and bile flow and there is an acknowledged association with the development of gallstones. The incidence of gallstone formation with octreotide treatment is estimated to be between 15 - 30 %.

Ultrasonic examination of the gallbladder, before and at about 6 to 12 month intervals during octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated in the normal manner with due attention to abrupt withdrawal of the drug.

In patients with cirrhosis, dosage adjustment may be necessary (see Section 4.2 Posology and Method of Administration).

4.5 Interaction with other medicinal products and other forms of interaction

Octreotide has been reported to reduce the intestinal absorption of cyclosporin and to delay that of cimetidine.

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

Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that 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. carbamazepine, digoxin, warfarin and terfenadine).

4.6 Pregnancy and lactation

Experience with octreotide in pregnant or nursing women is very limited, and they should therefore be given the drug only under compelling circumstances.

Women receiving treatment with octreotide should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

No data exists on the effects of octreotide on the ability to drive and use machines.

4.8 Undesirable effects

The main side-effects are local and gastrointestinal.

Body as a whole

Rare: hypersensitivity skin reactions; hair loss and isolated reports of anaphylactic reactions have been observed.

Cardiovascular system

Isolated cases of bradycardia.

Gastrointestinal system

Anorexia, nausea, vomiting, abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea and steatorrhea. Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption. In rare instances, gastrointestinal side-effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Occurrence of gastrointestinal side-effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed.

Hepatobiliary

Prolonged use of octreotide may result in gallstone formation (see 4.4 Special warnings and precautions for use), and there have been isolated cases of biliary colic following the abrupt withdrawal of the drug in acromegalic patients in whom biliary sludge or gallstones had developed.

There have been isolated reports of hepatic dysfunctions associated with octreotide administration. These consist of:

- acute hepatitis, without cholestasis, where transaminase values have normalised on withdrawal of octreotide, or
- slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma-glutamyl transferase and, to a lesser extent, transaminases.

Pancreas

Because of its inhibitory action on growth hormone, glucagon, and insulin release, octreotide may affect glucose regulation. Postprandial 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 observed within the first hours or days of octreotide treatment and resolves on withdrawal of the drug. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term octreotide treatment.

Local 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.

4.9 Overdose

Doses of up to 2000 microgrammes octreotide given as subcutaneous tid for several months have been well tolerated.

No life-threatening reactions have been reported after acute overdosage. The maximum single dose given to an adult so far has been 1 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, which resolved in 24 hours of drug administration.

One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (250 microgrammes per hour for forty eight hours instead of 25 microgrammes per hour). He experienced no side-effects.

The management of overdosage is symptomatic.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antigrowth hormones (ATC code H01B C02).

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

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

In normal healthy subjects octreotide, like somatostatin, has been shown to inhibit

- release of growth hormone stimulated by arginine, exercise and insulin-induced hypoglycaemia
- postprandial release of insulin, glucagon, gastrin other peptides of the gastroenteropancreatic system; arginine-stimulated release of insulin and glucagon and
- thyrotropin-releasing hormone (TRH) - stimulated release of thyroid stimulating hormone (TSH).

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

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

In patients with acromegaly, octreotide consistently lowers GH and normalises IGF-1 serum concentrations in the majority of patients. In most patients, octreotide markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue,

osteoarthralgia and carpal tunnel syndrome. In individual patients with GH-secreting pituitary adenoma, octreotide was reported to lead to shrinkage of the tumour mass.

For patients with functional tumours of the gastroenteropancreatic endocrine system, treatment with octreotide provides continuous control of symptoms related to the underlying disease. The effects of octreotide in different types of gastroenteropancreatic tumours are as follows:

Carcinoid tumours

Administration of octreotide may result in improvement of symptoms, particularly of flushing and diarrhoea. In many cases, this is accompanied by a falling 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 octreotide 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. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas

Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of octreotide 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. Octreotide produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of octreotide 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.

5.2 Pharmacokinetic properties

Absorption

After subcutaneous injection, octreotide 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 octreotide bound to blood cells is negligible.

Elimination

The elimination half-life after subcutaneous administrations is 100 minutes. After intravenous injection the elimination is biphasic with half-lives of 10 and 90 minutes respectively. About 32 % is excreted unchanged into the urine.

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Studies in animals showed transient growth retardation of offspring, possibly consequent upon the specific endocrine profiles of the species tested, but there was no evidence of foetotoxic, teratogenic, or other reproduction effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Phenol
Glacial acetic acid
Sodium chloride
Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

For prolonged storage, vials should be stored between 2°C and 8°C. For day-to-day use they may be stored at room temperature for up to two weeks. Protect from light. Do not freeze.

6.5 Nature and contents of container

5 ml ampoule of uncoloured glass containing clear colourless solution.
Boxes of 1 ampoules.

6.6 Special precautions for disposal

For i.v. use octreotide should be diluted with normal saline to a ratio of not less than 1 vol : 1 vol and not more than 1 vol : 9 vol . Dilution of octreotide with glucose solution is not recommended.

If octreotide has been diluted, the prepared solution may be kept at room temperature but should be administered within 8 hours of preparation.

To prevent contamination, it is recommended to puncture the cap of the vial not more than 10 times.

To reduce local discomfort, let the solution reach room temperature before injection. Avoid multiple injections at short intervals at the same site.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceuticals UK Limited
4/5 Loveridge Mews,
London NW6 2DP
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 24897/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/05/2008

10 DATE OF REVISION OF THE TEXT

12/05/2008

11 DOSIMETRY (IF APPLICABLE)**12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

PACKAGE LEAFLET: INFORMATION FOR THE USER**Octreotide 50 micrograms/ml Solution for Injection
Octreotide 100 micrograms/ml Solution for Injection
Octreotide 500 micrograms/ml Solution for Injection
Octreotide 200 micrograms/ml Solution for Injection
Octreotide**

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Octreotide Solution for Injection, is and what it is used for
2. Before you take Octreotide Solution for Injection
3. How to take Octreotide Solution for Injection
4. Possible side effects
5. How to store Octreotide Solution for Injection
6. Further information

1. What Octreotide Solution for Injection is and what it is used for

Octreotide is a synthetic version of the natural hormone somatostatin. Octreotide is used for the relief of symptoms associated with the over-production of some of the body's natural substances acting on the gut and hormone systems. Over-production of these substances upsets your natural hormone balance and causes a variety of signs and symptoms such as flushing, diarrhoea, low blood pressure, sweating, rash and weight loss.

Octreotide can also be used to reduce levels of growth hormone if you have acromegaly. Octreotide can help to improve symptoms caused by over-production of growth hormone such as headaches, sweating, tiredness and numbness and tingling in the hands and feet.

Octreotide can be used in some patients before they have an operation on the pancreas. The use of octreotide may reduce some of the problems which can occur in the abdomen after the operation, such as inflammation (swelling) and infection.

2. Before you take Octreotide Solution for Injection

Tell your doctor before you start taking octreotide if the answer to any of the following questions is yes:

- Do you suspect that you have had an allergic reaction to similar products, or any of the ingredients in Octreotide Solution for Injection (listed under "Further information"- "What Octreotide Solution for Injection contains")?
- Have you ever suffered from gallstones or other stomach problems?
- Are you a diabetic?
- Do you have any thyroid problems, or have you had a disease which may have affected your thyroid?
- Do you have any problems with your liver, or have you had a disease which may have affected your liver?
- Are you pregnant, or planning to become pregnant?
- If you do become pregnant whilst taking octreotide tell your doctor.
- Are you breastfeeding?
- Are you taking any other medicines (either bought or prescribed)?

Some medicines can interfere with your treatment, so make sure to check with your doctor or pharmacist before taking any other medicines. In particular, tell your doctor if

you are taking bromocriptine, cyclosporin, cimetidine or insulin.

The effect of some medicines metabolised by the liver can also be affected by octreotide, for example, carbamazepine, digoxin, warfarin and terfenadine, so tell your doctor or pharmacist about all the medicines you are taking.

3. How to take Octreotide Solution for Injection

Follow the instructions given to you by your doctor. He/she will tell you the correct dose and how often to inject your medicine. Follow your doctor's instructions exactly and never change the dose yourself. Ask your doctor or pharmacist if you are unsure about how much medicine to use or when to use it.

Your medicine must be injected subcutaneously, i.e., into the tissue under the skin. Your doctor or nurse will show you how to do this and if you are unsure return to them for advice. Use a clean, sterile syringe and needle every time and avoid multiple injections at short intervals at the same site.

In rare cases Octreotide Solution for Injection may have to be injected intravenously (into a vein). If this is necessary the doctor or nurse will perform the injection. You must NOT inject Octreotide Solution for Injection into your veins yourself.

Do not use the injection straight from the fridge.

Let it reach room temperature naturally first.

Do not open the ampoule until it is time to take your injection.

Please note that Octreotide Solution for Injection ampoules have a small etch at the breaking point of the ampoule together with a blue spot at the top of each ampoule. To snap open an ampoule, you should carefully apply thumb pressure from one hand to the blue spot at the top of the ampoule holding the lower half of the ampoule with your other hand.

For the relief of symptoms associated with the over-production of some of the body's natural substances, treatment is usually started with 50 micrograms once or twice daily by subcutaneous injection. Your doctor may feel it is necessary to gradually increase your dose, until your ideal dose is established. Follow your doctor's instructions carefully and do not change your dose unless your doctor tells you to.

For the treatment of acromegaly the usual dose is 100-200 micrograms three times a day by subcutaneous injection.

If you take more than you should:

If you accidentally use too much of your medicine, tell your doctor immediately or go to your nearest casualty department.

If you forget to take Octreotide Solution for Injection:

If you forget to inject a dose then inject another as soon as you remember, unless it is almost time for your next dose; then go on as before. Do NOT double your dose or inject two doses at once.

4. Possible Side Effects

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

Most people who are prescribed Octreotide Solution for Injection will benefit from taking it, but a few can be upset by it. If you are receiving this medicine on a long term basis then you will go to hospital from time to time to have regular check-ups. There is no need to worry if you suffer from any of the following reactions at the site of injection:

- Pain
- Sensation of stinging, tingling or burning
- Redness and swelling

PAP 0000

Size 188x220mm

These rarely last more than 15 minutes and are reduced by letting your medicine reach room temperature before injecting.

Octreotide sometimes causes:

- Weight loss
- Nausea, vomiting
- Stomach pain/bloating
- Wind
- Loose/"fatty" stools/diarrhoea
- Changes in blood sugar levels

These can be minimised by injecting Octreotide Solution for Injection between meals or before going to bed.

Octreotide sometimes causes:

- Gallstones

Octreotide has also been reported to rarely cause:

- Hair loss
- Allergic skin reactions
- Allergic type reactions including one or more of the following symptoms: flushing of face and/or general "hive" or "nettle" type reaction, chest tightness, shortness of breath, wheezing and faintness as a result of a fall in blood pressure
- A very slow pulse (under 60 beats per minute)

If you are concerned about any of these symptoms tell your doctor at your next visit.

If you develop any of the following see your doctor immediately:

- Prolonged/troublesome bloating of the stomach with pain
- Nausea/vomiting associated with drowsiness
- Restlessness
- Giddiness
- Yellowing of skin
- Yellowing of the whites of your eyes

Tell your doctor immediately if you have any other symptoms not mentioned in this leaflet.

Also growth hormone secreting pituitary tumours may sometimes expand and you should tell your doctor if you experience any problems with your eyes or sight.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Octreotide Solution for Injection

Keep out of reach and sight of children.

Store your medicine in a safe place where children cannot **see it or reach it**. Your medicine could harm them.

Do not use this medicine after the expiry date which is stated on the label. Expiry date refers to the last day of that month.

Store the ampoules and multidose vial in the fridge (between 2°C and 8°C) and protect from light in the original packaging. You can keep a few ampoules at room temperature away from direct heat but they will only last two weeks. If you do not use a whole ampoule return the remainder to your pharmacist.

Once in use, a multidose vial may be stored at room temperature away from direct heat for up to two weeks. You can use your multidose vial up to 10 times and you must return any remainder to your pharmacist if you have not used it within two weeks.

If your doctor decides to stop your treatment, return any left over medicine to the

pharmacist. Only keep it if your doctor tells you to.

Medicines should not be disposed off via wastewater or household waste. Ask your pharmacist how to dispose off medicines no longer required. These measures will help to protect the environment.

6. Further Information

What Octreotide Solution for Injection contains

Octreotide Solution for Injection is a colourless solution, and is available in ampoules of 3 strengths:

50 micrograms octreotide in 1 ml
100 micrograms octreotide in 1 ml
500 micrograms octreotide in 1 ml

Octreotide Solution for Injection is also available as a clear colourless solution in a multidose vial containing:
1 mg octreotide in 5 ml (provides 200 micrograms octreotide in 1 ml)

The active substance is octreotide, as octreotide acetate.

Octreotide Solution for Injection, 50 microgram/ml, 100 microgram/ml and 500 microgram/ml (in ampoules) also contain the following inactive ingredients: sodium acetate trihydrate, glacial acetic acid, sodium chloride, water for injections.

Octreotide Solution for Injection 200 microgram/ml (in multidose vials) also contains the same inactive ingredients as well as phenol.

Each strength of Octreotide Solution for Injection ampoules is available in packs of 5 ampoules. The multidose vials are available as packs of 1 vial.

Marketing Authorisation Holder:

Sun Pharmaceuticals UK Limited
4/5 Loveridge Mews, London NW6 2DP, UK.

Manufacturer:

Polar Speed Distribution Ltd
8 Chartmoor Road, Leighton Buzzard,
Bedfordshire LU7 4WG, UK.

This medicinal product is authorised in the Member States of the EEA under the following name

This leaflet was last approved in XXXX

ISS: 03/2008
PJPI 0000

Octreotide 50 micrograms/ml Injection
1 ml Ampoule
For sc or iv use
Protect from light.
Store between 2° and 8°C.

Market Authorisation Holder:
Sun Pharmaceuticals UK Limited
 4/5 Loveridge Mews,
 London NW6 2DP, U.K.

EXP:
 Batch No.:
 PL. No.: 24897 / 0001

PXLB 0107

Final Size: 30 x 20 mm
 Magnification: 400%
For UK

30 mm

20 mm

Open here 

Octreotide 50 micrograms/ml Injection 5 ampoules of 1 ml

Octreotide 50 micrograms/ml Injection 5 ampoules of 1 ml

Octreotide 50 micrograms/ml Injection 5 ampoules of 1 ml

Each ampoule contains octreotide acetate equivalent to 50 micrograms octreotide in 1 ml.
 Each ampoule also contains glacial acetic acid, sodium acetate trihydrate, sodium chloride and water for injection.

Solution for injection.
 Use as directed by your doctor.
 For further information see enclosed leaflet.

Store between 2° and 8°C.

Allow to reach room temperature before administration.

Protect from light.

Keep out of reach and sight of children.

PL No.: 24897 / 0001

Market Authorisation Holder:
Sun Pharmaceuticals UK Limited
 4/5 Loveridge Mews,
 London NW6 2DP, U.K.

 **POM**

EXP:
 Batch No.: 8901127007274



Octreotide 50 micrograms/ml Injection

5 ampoules of 1 ml







Octreotide 100 micrograms/ml Injection

1 ml Ampoule

For sc or iv use

Protect from light.


Store between 2° and 8°C.

Market Authorisation Holder:
Sun Pharmaceuticals UK Limited
4/5 Loveridge Mews,
London NW6 2DP, U.K.

EXP:
Batch No.:
PL. No.: 24897 / 0002

Final Size: 30 x 20 mm
Magnification: 400%
For UK

Open here



Octreotide 100 micrograms/ml Injection 5 ampoules of 1 ml

Each ampoule contains octreotide acetate equivalent to 100 micrograms octreotide in 1 ml.

Each ampoule also contains glacial acetic acid, sodium acetate trihydrate, sodium chloride and water for injection.

Solution for injection.

Use as directed by your doctor.

For further information see enclosed leaflet.

Store between 2° and 8°C.


Allow to reach room temperature before administration.

Protect from light.

Keep out of reach and sight of children.

PL. No.: 24897 / 0002

Market Authorisation Holder:
Sun Pharmaceuticals UK Limited
4/5 Loveridge Mews,
London NW6 2DP, U.K.




POM

Octreotide 100 microgram/ml Injection 5 ampoules of 1 ml


Batch No.: 8901127007281

EXP:




Octreotide 100 microgram/ml Injection 5 ampoules of 1 ml

Octreotide 100 micrograms/ml Injection



5 ampoules of 1 ml


Octreotide 100 microgram/ml Injection 5 ampoules of 1 ml



Octreotide 100 microgram/ml Injection 5 ampoules of 1 ml

Batch No.: 8901127007281

EXP:



Octreotide 100 microgram/ml Injection 5 ampoules of 1 ml

Final Size: 83 x 70 x 16 mm
For UK

Octreotide 500 micrograms/ml Injection
1 ml Ampoule
For sc or iv use
Protect from light.
Store between 2° and 8°C.

Market Authorisation Holder:
Sun Pharmaceuticals UK Limited
 4/5 Loveridge Mews,
 London NW6 2DP, U.K.

EXP:
 Batch No.:
 PL No.: 24897 / 0003

PXLB 0109

Final Size: 30 x 20 mm
 Magnification: 400%
 For UK

30 mm

20 mm

Open here 

Octreotide 500 micrograms/ml Injection 5 ampoules of 1 ml

Octreotide 500 micrograms/ml Injection 5 ampoules of 1 ml

Each ampoule contains octreotide acetate equivalent to 500 micrograms octreotide in 1 ml.

Each ampoule also contains glacial acetic acid , sodium acetate trihydrate, sodium chloride and water for injection.

Solution for injection.

Use as directed by your doctor.

For further information see enclosed leaflet.

Store between 2° and 8°C.

Allow to reach room temperature before administration.

Protect from light.

Keep out of reach and sight of children.

PL No.: 24897 / 0003

Market Authorisation Holder:
Sun Pharmaceuticals UK Limited
 4/5 Loveridge Mews,
 London NW6 2DP, U.K.



POM

Octreotide 500 micrograms/ml Injection 5 ampoules of 1 ml

Batch No.: 8901127007298
 EXP: 

Octreotide 500 micrograms/ml Injection

5 ampoules of 1 ml 





