SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Octreotide 500 micrograms/1 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is octreotide acetate.

Each mL of solution for injection contains 500 micrograms of octreotide as octreotide acetate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

Prevention of complications following pancreatic surgery.

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

Treatment of TSH-secreting pituitary adenomas:

- when secretion has not normalised after surgery and/or radiotherapy;
- in patients in whom surgery is inappropriate;
- in irradiated patients, until radiotherapy is effective.

4.2 Posology and method of administration

Posology

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

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

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

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

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

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

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

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

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

Use in children
Experience with Octreotide in children is limited.

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

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

Method of administration
Octreotide may be administered directly by subcutaneous (s.c.) injection or by intravenous (i.v.) infusion after dilution. For further instructions on handling and instructions for dilution of the medicinal product, refer to section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General

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

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

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

Hepatic function should be monitored during octreotide therapy.

Cardiovascular related events

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

Atrioventricular blocks (including complete atrioventricular block) were reported in patients receiving high doses of continuous infusion (100 micrograms/hour) and in patients receiving bolus octreotide intravenously (50 micrograms bolus followed by 50 micrograms/hour continuous infusion). The maximum dose of 50 micrograms/hour should therefore not be exceeded (see section 4.2). Patients who receive high doses of intravenous octreotide should be kept under appropriate cardiac monitoring.

Gallbladder and related events

Cholelithiasis is a very common event during octreotide treatment and may be associated with cholecystitis and biliary duct dilatation (see section 4.8). Ultrasonic examination of the gallbladder before, and at about 6- to 12-month intervals during Octreotide therapy is therefore recommended.

Pancreatic function

Pancreatic exocrine insufficiency (PEI) has been observed in some patients receiving octreotide therapy for gastroenteropancreatic neuroendocrine tumours. Symptoms of PEI can include steatorrhea, loose stools, abdominal bloating, and weight loss. Screening and appropriate treatment for PEI according to clinical guidelines should be considered in symptomatic patients.

GEP endocrine tumours

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

Glucose metabolism

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

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

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

Oesophageal varices

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

Local site reactions

In a 52-week toxicity study in rats, predominantly in males, sarcomas were noted at the s.c. injection site only at the highest dose (about 8 times the maximum human dose based on body surface area). No hyperplastic or neoplastic lesions occurred at the s.c. injection site in

a 52-week dog toxicity study. There have been no reports of tumour formation at the injection sites in patients treated with Octreotide for up to 15 years. All the information available at present indicates that the findings in rats are species specific and have no significance for the use of the drug in humans (see section 5.3).

Nutrition

Octreotide may alter absorption of dietary fats in some patients.

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

Sodium content
This medicinal product contains less than 1 mmol (23 mg) sodium per dose. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of octreotide in pregnant women, and in approximately one third of the cases the pregnancy outcome are unknown. The majority of reports were received after post-marketing use of octreotide and more than 50% of exposed pregnancies were reported in patients with acromegaly. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-1200 micrograms/day of Octreotide s.c. or 10-40 mg/month of octreotide powder and solvent for suspension for injection (intramuscular use). Congenital anomalies were reported in about 4% of pregnancy cases for which the

outcome is known. No causal relationship to octreotide is suspected for these cases.

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

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

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

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

Tabulated list of adverse reactions

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

Table 1 Adverse drug reactions reported in clinical studies

Gastrointestinal disorders	
Very common:	Diarrhoea, abdominal pain, nausea, constipation, flatulence
Common:	Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces
Nervous system disorders	
Very common:	Headache
Common:	Dizziness
Endocrine disorders	
Common:	Hypothyroidism, thyroid disorder (e.g. decreased TSH, decreased total T4, and decreased free T4)
Hepatobiliary disorders	
Very common:	Cholelithiasis
Common:	Cholecystitis, biliary sludge, hyperbilirubinaemia
Metabolism and nutrition disorders	
Very common:	Hyperglycaemia
Common:	Hypoglycaemia, impaired glucose tolerance, anorexia
Uncommon:	Dehydration
General disorders and administration site conditions	
Very common:	Injection site reactions
Common:	Asthenia
Investigations	
Common:	Elevated transaminase levels
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia
Respiratory disorders	
Common:	Dyspnoea
Cardiac disorders	
Common:	Bradycardia
Uncommon:	Tachycardia

Post-marketing

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

Table 2 Adverse drug reactions derived from spontaneous reports

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

Description of selected adverse reactions

Gallbladder and related reactions
Somatostatin analogues have been shown to inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Development of gallstones has been reported in 15 to 30% of long-term recipients of s.c. octreotide acetate. The incidence in the general population (aged 40 to 60 years) is 5 to 20%. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated either by dissolution therapy with bile acids or by surgery.

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

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

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

Hypersensitivity and anaphylactic reactions
Hypersensitivity and allergic reactions have been reported during post-marketing experience. When these occur, they mostly affect the skin, rarely the mouth and airways. Isolated cases of anaphylactic shock have been reported.

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

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

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

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

Thrombocytopenia
Thrombocytopenia has been reported during post-marketing experience, particularly during treatment with octreotide acetate (i.v.) in patients with cirrhosis of the liver. This is reversible after discontinuation of treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or

Apple App Store.

4.9 Overdose

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

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

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

Atrioventricular blocks (including complete atrioventricular block) were reported in patients receiving 100 micrograms/hour of continuous infusion and/or bolus octreotide intravenously (50 micrograms bolus followed by 50 micrograms/hour continuous infusion).

The management of overdosage is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatostatin and analogues, ATC code: H01CB02

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

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

In healthy subjects octreotide has been shown to inhibit:

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

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

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

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

Octreotide's effects in the different tumour types 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 fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid.

VIPomas

The biochemical characteristic of these tumours is overproduction of vasoactive intestinal peptide (VIP). In most cases, administration of 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. In some patients, computed tomography scanning suggests a slowing or arrest of progression of the tumour, or even tumour shrinkage, particularly of hepatic metastases. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas

Administration of 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.

Gastrinomas/Zollinger-Ellison syndrome

Therapy with proton pump inhibitors or H2 receptor blocking agents generally controls gastric acid hypersecretion. However, diarrhoea, which is also a prominent symptom, may not be adequately alleviated by proton pump inhibitors or H2 receptor blocking agents.

Octreotide can help to further reduce gastric acid hypersecretion and improve symptoms, including diarrhoea, as it provides suppression of elevated gastrin levels, in some patients.

Insulinomas

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

Complications following pancreatic surgery

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

Bleeding gastro-oesophageal varices

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

Treatment of TSH-secreting pituitary adenomas

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

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

5.2 Pharmacokinetic properties

Absorption

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

Special patient population

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

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

5.3 Preclinical safety data

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

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

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

Carcinogenicity/chronic toxicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid (pH adjustment),
Sodium acetate trihydrate (pH adjustment),
Sodium chloride,
Water for injections.

6.2 Incompatibilities

The octreotide acetate is not stable in Total Parenteral Nutrition (TPN) solutions.

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

Medicinal product as packaged for sale: 3 years
Shelf-life after first opening: The product must be used immediately and any unused drug-product must be discarded

6.4 Special precautions for storage

Medicinal product as packaged for sale: store in a refrigerator (2°C - 8ºC).
Do not freeze. Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.6.

6.5 Nature and contents of container

2 mL Type I amber glass vials for injection, with a teflon-faced rubber stopper, aluminium seal and flip-off plastic cap, containing 1 mL of Octreotide solution for injection.
Packs of 5 and 30 vials containing 1 mL of solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Each vial contains a clear colourless solution, free from foreign matter.

Single dose vials (50 micrograms/1 mL, 100 micrograms/1 mL and 500 micrograms/1 mL injection) are for single use only.

Subcutaneous injections
Patients who will be injecting themselves must receive precise instructions from the doctor or nurse.
To reduce local discomfort, let the solution reach room temperature before injection.
Avoid multiple injections at short intervals at the same site.
To prevent contamination, it is recommended that the cap of the multidose vial (200 micrograms/mL) should be punctured no more than 10 times.

Intravenous infusion

Prior to administration the solution should be inspected visually for changes of colour or solid particles. The diluted solutions of Octreotide (octreotide acetate) in sodium chloride 9 mg/mL (0.9%) solution for injection and stored in PVC bags or in polypropylene syringes are physically and chemically stable for seven days when stored at below 25°C. From a microbiological point of view, the diluted solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the user and normally should not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Before administration the solution has to be brought to room temperature again.

When Octreotide is to be administered as intravenous infusion, the contents of one 500 micrograms vial should normally be dissolved in 60 mL physiological saline, and the resulting solution should be infused by means of an infusion pump. This should be repeated as often as necessary until the prescribed duration of treatment is reached. Octreotide has also been infused in lower concentrations.

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

7. MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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