Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Octreotide Bendalis 0.05 mg/ml
Octreotide Bendalis 0.1 mg/ml
Octreotide Bendalis 0.5 mg/ml
Octreotide Bendalis 0.2 mg/ml

Solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Octreotide Bendalis *0.05 mg/ml*:
1 ampoule with 1 ml contains 50 μg Octreotide (as Octreotide acetate).

Octreotide Bendalis *0.1 mg/ml*:
1 ampoule with 1 ml contains 100 μg Octreotide (as Octreotide acetate).

Octreotide Bendalis *0.5 mg/ml*:
1 ampoule with 1 ml contains 500 μg Octreotide (as Octreotide acetate).

Octreotide Bendalis *0.2 mg/ml*:
1 vial with 5 ml contains 1000 μg Octreotide (200 μg/ml) (as Octreotide acetate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment and reduction of growth hormone (GH) and IGF-1 plasma levels in patients with acromegaly inadequately controlled by surgery or radiotherapy. Octreotide Bendalis is also indicated for acromegalic patients unable or unwilling to undergo surgery, or in the initial stage until radiotherapy becomes fully effective.

Treatment of symptoms associated with functional gastro-enteropancreatic (GEP) endocrine tumours, e.g. carcinoid tumours with features of a carcinoid syndrome (see section 5.1).

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

Prevention of complications following pancreatic surgery.

Emergency management to stop bleeding and to prevent re-bleeding from gastro-oesophageal varices in patients with cirrhosis. In such cases, Octreotide Bendalis is to be used in conjunction with specific treatment such as endoscopic sclerotherapy.

Treatment of TSH-secreting pituitary adenomas:
- when secretion has not returned to normal 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 Octreotide subcutaneously every 8 to 12 hours. The dosage should be adjusted 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. In patients on a stable dose of Octreotide Bendalis, the GH levels should be assessed every six months.

If there has been no relevant reduction in GH levels and no improvement in the clinical symptoms within three months of starting treatment with Octreotide Bendalis, therapy should be discontinued.

Gastroenteropancreatic endocrine tumours
The initial dose is 0.05 mg subcutaneously once or twice daily. Depending on the clinical response, the effect on levels of tumour-produced hormones (in case of carcinoid tumours, on the urinary excretion of 5-hydroxyindole acetic acid) and on tolerability, the dosage can be gradually increased to 0.1–0.2 mg three times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses must be adjusted individually.

In carcinoid tumours, therapy should be discontinued if there is no improvement after one week of treatment at the maximum tolerated dose.

Prevention of complications following pancreatic surgery
The dose is 0.1 mg three times daily as a subcutaneous injection for seven consecutive days, starting on the day of surgery at least one hour before laparotomy.

Bleeding from gastro-oesophageal varices
0.025 mg/hour for five days as a continuous intravenous infusion. Octreotide Bendalis can be used in dilution with physiological saline.

In cirrhotic patients with bleeding gastro-oesophageal varices, Octreotide Bendalis has been tolerated well at continuous intravenous doses of up to 0.050 mg/hour for five days.

Use in the elderly
In elderly patients treated with Octreotide Bendalis, there were no indications of reduced tolerance or a need for dose adjustment.

Use in children
There is limited experience with the use of Octreotide Bendalis in children.

Use in patients with impaired hepatic function
In patients with liver cirrhosis, the half-life of the medicinal product may be increased, necessitating adjustment of the maintenance dose.

Use in patients with impaired renal function
Impaired renal function did not affect the total exposure (AUC) to Octreotide following subcutaneous injection, therefore no dose adjustment of Octreotide Bendalis is necessary.

Method of administration

Octreotide Bendalis 0.05 mg/ml, Octreotide Bendalis 0.1 mg/ml, Octreotide Bendalis 0.5 mg/ml may be administered directly as a subcutaneous (s.c.) injection or intravenous (i.v.) infusion after dilution. For further instructions on handling and dilution of the medicinal product, see section 6.6.

4.3 Contraindications

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 there is evidence of tumour expansion, 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 could potentially restore fertility in female acromegalic patients. Women 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 events
There have been frequent reports of bradycardia. The dose of medicinal products such as beta blockers, calcium channel blockers, or agents for controlling the fluid and electrolyte balance, may need to be adjusted (see section 4.5).

Gallbladder and related events
Cholelithiasis is a very common event during Octreotide Bendalis treatment and may be associated with cholecystitis and biliary duct dilatation (see section 4.8). Additionally, cases of cholangitis have been reported as a complication of cholelithiasis in patients taking Octreotide Bendalis in the post-marketing setting. Ultrasonic examination of the gallbladder before, and at about 6- to 12-month intervals during Octreotide Bendalis therapy is therefore recommended.

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

Glucose metabolism
Given its inhibitory effect on growth hormone, glucagon and insulin, Octreotide Bendalis may influence glucose regulation. Post-prandial glucose tolerance may be impaired and, in some instances, a state of persistent hyperglycaemia may result from chronic administration. Hypoglycaemia has also been reported.

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, Octreotide may increase the intensity and duration of hypoglycaemia in patients with insulinomas. These patients must be closely monitored at the start of Octreotide Bendalis therapy and whenever the dose is modified. Marked fluctuations in blood glucose concentration may possibly be reduced by smaller, more frequently administered doses.

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

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

Local injection site reactions
In a 52-week toxicity study in rats (predominantly male), sarcomas were noted at the subcutaneous injection site only at the highest dose, which was about eight times the maximum human dose based on body surface area. No hyperplastic or neoplastic lesions occurred at the subcutaneous injection site in a 52-week toxicity study in dogs. There have been no reports of tumour formation at the subcutaneous injection site in patients treated with Octreotide Bendalis for up to 15 years. All the information available at present indicates that the findings in rats are species-specific and are not relevant to the use of the medicinal product in humans (see section 5.3).

Nutrition
Octreotide may alter the absorption of dietary fats in some patients.

Reduced vitamin B12 levels and abnormal Schilling's test results have been observed in some patients receiving Octreotide therapy. Monitoring of vitamin B12 levels is recommended during treatment with Octreotide Bendalis in patients who have a history of vitamin B12 deficiency.

Sodium content:
Octreotide Bendalis contains sodium, but no more than 1 mmol (23 mg) per dose, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The dose of medicinal products such as beta blockers, calcium channel blockers, or agents for controlling the fluid and electrolyte balance, may need to be adjusted when Octreotide Bendalis is administered concomitantly (see section 4.4).

The dose of insulin and antidiabetic agents may need to be adjusted during concurrent administration of Octreotide Bendalis (see section 4.4).

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

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

Limited published data indicate that somatostatin analogues may decrease the metabolic clearance of compounds metabolised by cytochrome P450 enzymes, possibly due to the suppression of growth hormone. As Octreotide cannot be excluded as a cause of this effect, other medicinal products which are primarily metabolised by CYP3A4 and have a low therapeutic index (e.g. quinidine, terfenadine) should be administered with caution.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is only very limited experience (fewer than 300 pregnancy outcomes) from the use of Octreotide in pregnant women, and in approximately one third of the cases the pregnancy outcomes are unknown. The majority of reports were spontaneous, and more than 50 % of the pregnancies involved patients with acromegaly. Most women were exposed to Octreotide during the first trimester of pregnancy at doses of 100-1200 micrograms/day of Octreotide Bendalis s.c. or 10-40 mg/month of Octreotide Bendalis. Congenital anomalies were reported in about 4 % of pregnancies for which the outcome is known. No causal relationship with Octreotide is suspected in these cases.

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

As a precautionary measure, use of Octreotide Bendalis should be avoided during pregnancy (see section 4.4).

Breast-feeding
It is not known whether Octreotide is excreted in human milk. Animal studies have demonstrated that Octreotide is excreted in breast milk. Patients should not breast-feed during treatment with Octreotide Bendalis

Fertility
It is not known whether Octreotide has an influence on human fertility. Late descent of the testes was found in the male offspring of dams treated during pregnancy and lactation. However, Octreotide 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 Bendalis has no or only a negligible influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience dizziness, asthenia/fatigue, or headache during treatment with Octreotide Bendalis.

4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions reported during Octreotide Bendalis treatment include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported adverse reactions in clinical trials with Octreotide 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 free T4), loose stools, decreased glucose tolerance, vomiting, asthenia, and hypoglycaemia.

Tabulated list of undesirable effects
The following adverse drug reactions, listed in Table 1, have been documented in clinical studies with Octreotide. The adverse drug reactions in Table 1 are grouped and ranked in descending order of frequency 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, the undesirable effects are ranked in order of decreasing severity.

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:	Vertigo
Endocrine disorders	
Common:	Hypothyroidism, thyroid dysfunction (e.g. decreased TSH, decreased total T4 and decreased free T4)
Hepatobiliary disorders	
Very common:	Cholelithiasis
Common:	Cholecystitis, biliary sludge, hyperbilirubinaemia
Metabolism and nutrition disorders	
Very common:	Hyperglycaemia
Common:	Hypoglycaemia, impaired glucose tolerance, anorexia 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, thoracic and mediastinal disorders	
Common:	Dyspnoea
Cardiac disorders	
Common:	Bradycardia
Uncommon:	Tachycardia

Post-marketing
The undesirable effects presented in Table 2 were reported spontaneously, and it is not always possible to reliably establish the frequency or 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 Arrhythmia
Investigations Elevated alkaline phosphatase levels, elevated gamma-glutamyl transferase levels

Description of selected adverse reactions

Gallbladder and related reactions
Octreotide Bendalis 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 Bendalis. The incidence in the general population (aged 40 to 60 years) is 5 to 20 %. If gallstones do occur, they 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 side effects is known to decrease over time under continued treatment.

The occurrence of gastrointestinal side effects may be reduced by avoiding meals around the time of subcutaneous administration of Octreotide Bendalis, i.e. by injecting between meals or on retiring to bed.

Local injection site reactions
Local reactions such as pain or a sensation of prickling, tingling or burning accompanied by redness and swelling at the injection site rarely last more than 15 minutes and can be reduced by allowing the Octreotide Bendalis solution to reach room temperature before injection, or by injecting a smaller volume of 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 from malabsorption.

Pancreatic enzymes
In very rare instances, acute pancreatitis has been reported within the first few hours or days of subcutaneous Octreotide Bendalis treatment and resolved on discontinuation of the medicinal product. In addition, cholelithiasis-induced pancreatitis has been reported in patients on long-term subcutaneous Octreotide Bendalis treatment.

Cardiac disorders
Bradycardia is a common adverse reaction with somatostatin analogues. In both acromegalic and carcinoid syndrome patients, ECG changes such as QT prolongation, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes have been observed. No relationship has been established between these events and Octreotide because many of these patients had underlying cardiac diseases (see section 4.4).

Thrombocytopenia
Thrombocytopenia has been reported during post-marketing experience, particularly during treatment with Octreotide Bendalis (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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

A limited number of accidental overdoses of Octreotide Bendalis 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 daily). The adverse effects reported were arrhythmia, hypotension, cardiac arrest, cerebral 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 reported adverse effect was mild hyperglycaemia.

No unexpected adverse effects have been reported in cancer patients receiving Octreotide Bendalis at doses of 3,000 – 30,000 micrograms/day (divided into several subcutaneous doses).

Treatment of overdose should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatostatin and analogues, ATC code: H01CB02

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

In animals, Octreotide inhibits the release of growth hormone, glucagon and insulin more powerfully than somatostatin, with greater selectivity for GH and glucagon suppression.

In healthy individuals, Octreotide Bendalis has demonstrated the following effects:
- Inhibition of the release of GH stimulated in different ways (arginine, exertion, and insulin-induced hypoglycaemia)
- Inhibition of the postprandial release of insulin, glucagon, gastrin and other peptides of the GEP system, and of the arginine-stimulated secretion of insulin and glucagon
- Inhibition of the release of thyrotropin-releasing hormone (TRH) (inducing the release of thyroid-stimulating hormone (TSH))

Unlike somatostatin, Octreotide primarily inhibits insulin-induced GH secretion and does not result in a rebound phenomenon (hypersecretion of GH in patients with acromegaly).

In patients with acromegaly, Octreotide Bendalis lowers the plasma levels of GH and IGF-1. A reduction of GH 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 50 % of cases. In most patients Octreotide Bendalis markedly improves the clinical symptoms such as headache, skin and soft-tissue swelling, hyperhidrosis, arthralgia and paraesthesia. In patients with a large pituitary adenoma, Octreotide Bendalis treatment may reduce the volume of the tumour tissue to a certain extent.

In patients with functional tumours of the gastroenteropancreatic endocrine system, Octreotide Bendalis may improve the clinical picture due to its diverse endocrinal effects. Clinical and symptomatic improvements can be achieved in patients who continue to experience tumour-induced symptoms despite previous treatment (surgery; hepatic artery embolisation; e.g. with streptozocin and 5-fluorouracil).

Octreotide Bendalis exerts the following effects in different tumour types:

Carcinoid tumours
Administration of Octreotide Bendalis will generally improve the symptoms, particularly flushing and diarrhoea. In many cases, this will be accompanied by a drop in plasma serotonin and reduced urinary excretion of 5-hydroxyindoleacetic acid.

VIPomas
The biochemical feature of these tumours is the overproduction of vasoactive intestinal peptide (VIP). In most cases, administration of Octreotide Bendalis will alleviate the severe secretory diarrhoea typical of the condition and consequently improve quality of life. This will be accompanied by an improvement in the attendant electrolyte disorders, e.g. hypokalaemia, permitting discontinuation of enteral and parenteral fluid and electrolyte supplementation. In some patients, computed tomography imaging may suggest that tumour progression has slowed or stopped, or that the size
of the tumour has decreased, particularly in the case of hepatic metastases. The clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may return to the normal reference range.

Glucagonomas
Treatment with Octreotide Bendalis in most cases substantially improves the necrolytic migratory rash which is characteristic of this condition. The effect of Octreotide Bendalis on mild forms of diabetes mellitus, which frequently occur in patients with glucagonoma, is not pronounced; the need for insulin or oral hypoglycaemic agents generally is not reduced. Octreotide Bendalis improves diarrhoea, resulting in weight gain. Although treatment with Octreotide Bendalis often leads to an immediate reduction in plasma glucagon levels, this decrease generally is not maintained over a prolonged treatment period. Symptomatic improvement is sustained, however.

Gastrinomas/Zollinger-Ellison syndrome
Therapy with proton pump inhibitors or H2 receptor blocking agents will generally control 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 Bendalis can help to further reduce gastric acid hypersecretion and improve symptoms, including diarrhoea, as it suppresses elevated gastrin levels in some patients.

Insulinomas
Administration of Octreotide Bendalis leads to a decrease in the level of circulating immunoreactive insulin, but possibly only for a short period (about two hours). In patients with operable tumours, Octreotide Bendalis may help to restore and maintain normoglycaemia preoperatively. In patients with inoperable benign or malignant tumours, glycaemic control may be improved without a concomitant, sustained reduction in circulating insulin levels.

GRFomas
These rare tumors are characterized by production of GH releasing factor (GRF) alone or in conjunction with other active peptides. Octreotide Bendalis produces improvement in the features and symptoms of the resultant acromegaly. This is probably due to inhibition of GRF and GH secretion, and a reduction in pituitary enlargement may follow

Prevention of complications following pancreatic surgery
In patients who must undergo pancreatic surgery, the peri- and postoperative administration of Octreotide Bendalis reduces the incidence of typical postoperative complications (e.g. pancreatic fistula, abscess followed by sepsis, postoperative acute pancreatitis).

Bleeding from gastro-oesophageal varices
In patients with bleeding from gastro-oesophageal varices due to underlying cirrhosis, Octreotide Bendalis combined with specific treatment (e.g. sclerotherapy) results in better control of bleeding and early re-bleeding, and is associated with lower transfusion requirements and improved 5-day survival. While the precise mode of action of Octreotide Bendalis has not been fully explained, it is postulated that Octreotide Bendalis reduces splanchnic blood flow by inhibiting vasoactive hormones (e.g. VIP, glucagon).

5.2 Pharmacokinetic properties

Absorption
After subcutaneous injection, Octreotide Bendalis is rapidly and completely absorbed. Maximum plasma concentrations are reached within 30 minutes.

Subcutaneous administration is bioequivalent to intravenous application. Absolute bioavailability after subcutaneous administration has been calculated at 110 % ± 24 %.

Distribution
The volume of distribution is 0.27 l/kg and total clearance 160 ml/min. Plasma protein binding constitutes approx. 65 %. The quantity of Octreotide Bendalis bound to blood cells is negligible.

Elimination
The elimination half-life after subcutaneous administration is 100 minutes. After intravenous injection elimination is biphasic, with half-lives of 10 and 90 minutes. Most of the peptide is eliminated in the faeces, while approximately 32 % is excreted unchanged in the urine.

Special patient populations
Impaired renal function did not affect the total exposure (AUC) to Octreotide after subcutaneous injection.

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

5.3 Preclinical safety data

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

Reproduction studies in animals revealed no evidence of teratogenic, embryofoetal or other reproduction effects due to Octreotide after 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 pre- and post-natal developmental studies, reduced growth and maturation were observed in the F1 offspring of dams given Octreotide throughout pregnancy and lactation. Delayed descent of the testes was observed in male F1 offspring, but the fertility of the affected F1 male pups remained normal. Thus, the above-mentioned observations were transient and considered to be the consequence of GH inhibition.

Carcinogenicity/chronic toxicity
In rats given Octreotide acetate at daily doses of up to 1.25 mg/kg body weight, fibrosarcomas were observed at the s.c. injection site after 52, 104 and 113/116 weeks, predominantly in a number of male animals. Local tumours also occurred in the controls. However, development of these tumours was attributed to impaired fibroplasia caused by persisting irritative effects at the injection site and augmented by the acidic lactic acid/mannitol vehicle. This non-specific tissue reaction appeared to develop in rats in particular. Neoplastic lesions were not observed either in mice receiving daily s.c. injections of Octreotide at doses of up to 2 mg/kg for 98 weeks, or in dogs treated with daily s.c. doses of the medicinal product for 52 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Lactic acid
Sodium hydrogen carbonate
Phenol (only in Octreotide Bendalis *0.2 mg/ml*)
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Octreotide acetate does not remain stable in solutions for parenteral nutrition.

6.3 Shelf life

Octreotide Bendalis *0.05 mg/ml*, Octreotide Bendalis *0.1 mg/ml*, Octreotide Bendalis *0.5 mg/ml*
5 years

Octreotide Bendalis *0.2 mg/ml*
4 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.
Store in a refrigerator (2 °C – 8 °C).

Octreotide Bendalis *0.05 mg/ml*, Octreotide Bendalis *0.1 mg/ml*, Octreotide Bendalis *0.5 mg/ml*
For daily use, the ampoules of Octreotide Bendalis 0.05 mg/ml, Octreotide Bendalis 0.1 mg/ml and Octreotide Bendalis 0.5 mg/ml may be stored at room temperature for up to 2 weeks in the original package.
The ampoules must be used immediately after opening. Discard any remaining solution after opening.

Octreotide Bendalis *0.2 mg/ml*
Vials of Octreotide Bendalis 0.2 mg/ml may only be removed from the refrigerator for preparation of an injection. Between injections, they must be kept in the refrigerator at 2 °C – 8 °C in the original package.
The product remains stable for two weeks after opening.

Diluted solutions must be used immediately after reconstitution.

6.5 Nature and contents of container

Ampoules or vials consisting of clear glass (type I).

Octreotide Bendalis 0.05 mg/ml, *Octreotide Bendalis 0.1 mg/ml*, *Octreotide Bendalis 0.5 mg/ml*
Ampoules containing 1.0 ml solution for injection each.
Packs of 5 ampoules or 30 ampoules.

Octreotide Bendalis 0.2 mg/ml
Vials containing 5.0 ml solution for injection each.
Packs of 1 or 10 vials.

6.6 Special precautions for disposal and other handling

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

Instructions for use
Octreotide Bendalis *0.05 mg/ml*, Octreotide Bendalis *0.1 mg/ml*, Octreotide Bendalis *0.5 mg/ml*
The ampoules are intended for single use only. They may only be opened immediately before use. Any unused product must be discarded.

Octreotide Bendalis *0.2 mg/ml*
The vials are intended for multiple use. To prevent contamination, it is recommended to puncture the cap of the vial no more than 10 times.

Subcutaneous administration
Octreotide Bendalis should be used undiluted in case of subcutaneous administration.
Patients who are to self-administer the drug by subcutaneous injection must receive precise directions from their doctor or nurse.
To reduce local discomfort, it is recommended that the solution should be at room temperature before injection. Multiple injections at the same site at short intervals should be avoided.

Intravenous use
Parenteral medicinal products should be inspected visually for discolouration and particulate matter prior to administration. The product must be diluted prior to intravenous infusion. Octreotide Bendalis (Octreotide acetate) remains physically and chemically stable for 24 hours in sterile physiological saline solution or sterile solutions of 5 % dextrose (glucose) in water. However, as Octreotide Bendalis can affect glucose homeostasis, physiological saline solutions are recommended rather than dextrose. The diluted solutions remain physically and chemically stable for at least 24 hours below 25 °C. For microbiological reasons, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The content of one 0.5 mg ampoule should normally be diluted in 60 ml physiological saline, and the resulting solution administered with the aid of an infusion pump. This should be repeated as often as necessary until the prescribed duration of treatment is achieved.

7. MANUFACTURER

Bendalis GmbH
Keltenring 17
82041 Oberhaching
Germany

8. REGISTRATION HOLDER

David Margalit & Co. Ltd.
P.O.Box 16666 Tel Aviv

9. PRODUCT REGISRATION NO.:

Octreotide Bendalis 0.05 mg/ml
164-14-34086

Octreotide Bendalis 0.1 mg/ml
164-15-34084

Octreotide Bendalis 0.5 mg/ml
164-17-34083

Octreotide Bendalis 0.2 mg/ml
164-16-34085

Revised in August 2021