PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

OCTREOTIDE TEVA 10

OCTREOTIDE TEVA 20

OCTREOTIDE TEVA 30

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

One vial contains 10 mg, 20 mg or 30 mg octreotide (as octreotide acetate).

OCTREOTIDE TEVA 10:

Contains sugar (mannitol):

Powder for suspension: 41 mg mannitol per vial.

Suspension vehicle: 12 mg mannitol per 2 ml.

Reconstituted solution: 53 mg mannitol per vial.

OCTREOTIDE TEVA 20:

Contains sugar (mannitol):

Powder for suspension: 81,9 mg mannitol per vial.

Suspension vehicle: 12 mg mannitol per 2 ml.

Reconstituted solution: 93,9 mg mannitol per vial.

OCTREOTIDE TEVA 30:

Contains sugar (mannitol):

Powder for suspension: 122,9 mg mannitol per vial.

Suspension vehicle: 12 mg mannitol per 2 ml.

Reconstituted solution: 134,9 mg mannitol per vial.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Prolonged release suspension for injection.

Parenteral depot in the form of biodegradable microspheres.

4. CLINICAL PARTICULARS:

4.1. Therapeutic indications:

Treatment of patients with acromegaly:

- who are adequately controlled on subcutaneous (s.c) treatment with a somatostatin analogue
- in whom surgery or radiotherapy is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective (see **section 4.2**)

Treatment of patients with carcinoid tumours with:

- features of the carcinoid syndrome, in whom symptoms are adequately controlled on subcutaneous treatment with octreotide.
- VIPomas

4.2. Posology and method of administration:

Posology:

OCTREOTIDE TEVA may only be administered by deep intragluteal injection. The site of repeat intragluteal injections should be alternated between the left and the right gluteal muscle (see **Instructions for use/ handling**).

Acromegaly:

For patients who are adequately controlled with s.c. octreotide, it is recommended to start treatment with the administration of OCTREOTIDE TEVA 20 at 4-week intervals for 3 months. Treatment with

OCTREOTIDE TEVA 20 can be started on the day after the last dose of s.c. octreotide. Subsequent dosage adjustment should be based on serum growth hormone (GH) and insulin-like growth factor 1/somatomedin C (IGF 1) concentrations and clinical symptoms.

For patients in whom, within this 3-month period, clinical symptoms and biochemical parameters (GH; IGF 1) are not fully controlled (GH concentrations still above 2,5 microgram/L), the dose may be increased to 30 mg every 4 weeks. If after 3 months, GH, IGF 1, and/or symptoms are not adequately controlled at a dose of 30 mg, the dose may be increased to 40 mg every 4 weeks.
For patients whose GH concentrations are consistently below 1 microgram/L whose IGF 1 serum concentrations normalised and in whom most reversible signs/symptoms of acromegaly have disappeared after 3 months of treatment with 20 mg, 10 mg OCTREOTIDE TEVA may be administered every 4 weeks. However particularly in this group of patients it is recommended to closely monitor adequate control of serum GH and IGF 1 concentrations and clinical signs/symptoms at this low dose of OCTREOTIDE TEVA.
For patients on a stable dose of OCTREOTIDE TEVA assessment of GH and IFG 1 should be made every 6 months. For patients in whom surgery or radiotherapy is inappropriate or ineffective, or in the interim period until radiotherapy becomes fully effective, a short test dosing period of s.c. administration of octreotide is recommended to assess the response and systemic tolerability of octreotide prior to initiating treatment with OCTREOTIDE TEVA as described above.

Carcinoid tumours*:*

For patients in whom symptoms are adequately controlled with s.c. octreotide, it is recommended to start treatment with the administration of OCTREOTIDE TEVA 20 at 4-week intervals. The treatment with s.c. octreotide should be continued at the previously effective dosage for 2 weeks after the first injection of OCTREOTIDE TEVA 20.
For patients who were not previously treated with s.c. octreotide, it is recommended to start with the administration of s.c. octreotide at a dosage of 0,1 mg three times daily for a short period

(approximately 2 weeks) to assess the response and systemic tolerability of octreotide before initiating the treatment with OCTREOTIDE TEVA as described above.

For patients in whom symptoms and biological markers are well controlled after 3 months of treatment, the dose may be reduced to 10 mg OCTREOTIDE TEVA every 4 weeks

For patients in whom symptoms are only partially controlled after 3 months of treatment, the dose may be increased to 30 mg OCTREOTIDE TEVA every 4 weeks.

For days when symptoms associated with carcinoid tumours may increase during treatment with OCTREOTIDE TEVA, additional administration of s.c. octreotide is recommended at the dose used prior to the OCTREOTIDE TEVA treatment. This may occur mainly in the first 2 months of treatment until therapeutic concentrations of octreotide are reached.

Use in patients with impaired renal function:

No dose adjustment of OCTREOTIDE TEVA is necessary.

Use in patients with impaired hepatic function:

No data in patients with impaired hepatic function is available.

Use in elderly patients:

No data is available.

Use in children:

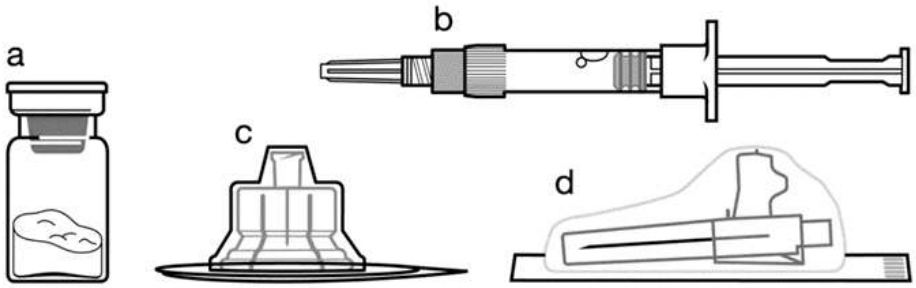
Safety and efficacy of OCTREOTIDE TEVA in children have not been established.

Method of administration:

Instructions for preparation and intramuscular injection of OCTREOTIDE TEVA.

FOR DEEP INTRAGLUTEAL INJECTION ONLY

Contents of the injection kit:



a One vial containing OCTREOTIDE TEVA powder

b One prefilled syringe containing the vehicle solution for reconstitution

c One vial adapter for drug product reconstitution

d One safety injection needle

Follow the instructions below carefully to ensure proper reconstitution of OCTREOTIDE TEVA before deep intragluteal injection.

There are 3 critical actions in the reconstitution of OCTREOTIDE TEVA. **Not following them could result in failure to deliver the medicine appropriately.**

- **The injection kit must reach room temperature**. Remove the injection kit from the fridge and let the kit stand at room temperature for a minimum of 30 minutes before reconstitution, but do not exceed 24 hours.
- After adding the diluent solution, **ensure that the powder is fully saturated** by letting the vial stand for 5 minutes.
- After saturation, **shake the vial moderately** in a horizontal direction for a minimum of 30 seconds **until a uniform suspension** is formed. The OCTREOTIDE TEVA suspension must only be prepared **immediately** before administration.

OCTREOTIDE TEVA should only be administered by a trained healthcare professional.

Step 1

Take the OCTREOTIDE TEVA injection kit out of the refrigerated storage in order to ensure it reaches room temperature. Plan approximately 30 to 60 minutes for acclimatisation but do not exceed 24 hours. Wash your hands with soap and hot water. Place the package on a clean and flat surface. Peel off the lid film from the blister tray containing the injection kit.

Note: The injection kit can be refrigerated if needed.

Step 2

Remove the plastic cap from the vial and clean the rubber stopper of the vial with an alcohol swab.

Note: Do not touch the rubber stopper after it has been cleaned. Peel the blister film and remove the vial adapter from its packaging by holding between the white luer cap and the skirt. DO NOT touch the tip of the access device at any place.

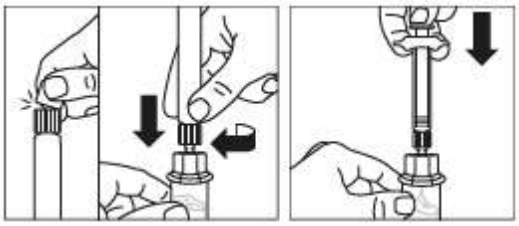
Position the vial adapter on top of the vial and push it fully down so that it snaps in place onto the vial, confirmed by an audible “click”.

Clean the tip of the vial adapter with an alcohol wipe.

Step 3

Pull-off the cap from the prefilled syringe containing the vehicle solution and screw the syringe onto the vial adapter.

Slowly push the plunger all the way down to transfer all the vehicle solution in the vial.



Step 4 ATTENTION: It is essential to let the vial stand for 5 minutes to ensure that the vehicle has fully saturated the powder. At this stage, prepare the patient for injection.

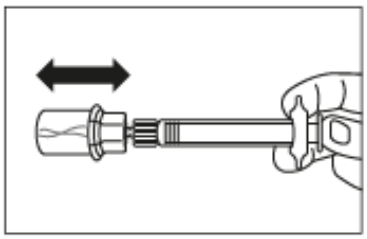
Note: It is normal if the plunger rod moves up as there might be a slight overpressure in the vial.

Step 5 After the saturation period, press the plunger all the way back in the syringe.

ATTENTION: Keep the plunger pressed and shake the vial **moderately** in a horizontal direction for a minimum of 30 seconds.

Check visually that the powder is completely suspended in the vehicle (uniform milky suspension).

Repeat shaking for further 30 seconds if the powder is not completely suspended.

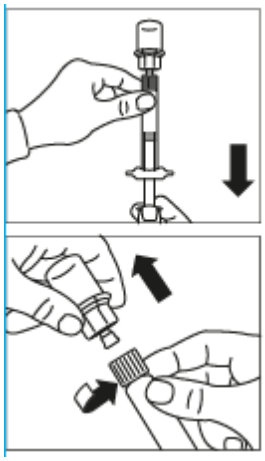


Step 6

Turn syringe and vial upside down, slowly pull the plunger out and draw the entire content from the vial into the syringe.

Unscrew the syringe from the vial adapter.

Administration must occur immediately after reconstitution.



Step 7

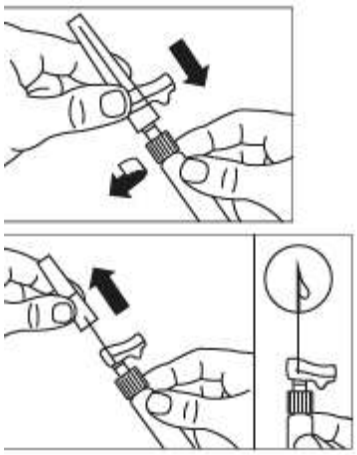
Screw the safety injection needle onto the syringe.

Pull the protective cover straight off the needle.

Gently invert the syringe to maintain a uniform suspension.

Gently tap the syringe to remove any visible bubbles and expel them from the syringe. Verify that the injection site has not been contaminated.

The reconstituted OCTREOTIDE TEVA is now ready for immediate administration. **Any delay may result in sedimentation.**



Step 8

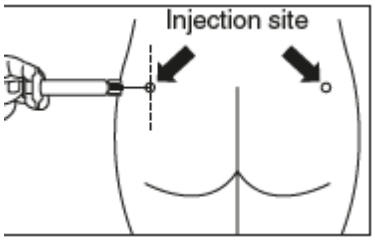
OCTREOTIDE TEVA must be given only by deep intragluteal injection, NEVER intravenously.

Clean the injection site with an alcohol swab.

Insert the needle fully into the right or left gluteus at a 90° angle to the skin.

Slowly draw back the plunger rod to check that no blood vessel has been penetrated, otherwise change the needle position.

Depress the plunger with steady pressure until the syringe is empty. After completing the injection, withdraw the needle from the injection site and activate the safety guard as shown in Step 9 below.



Step 9

Activate the safety guard over the needle in one of the 2 methods shown:

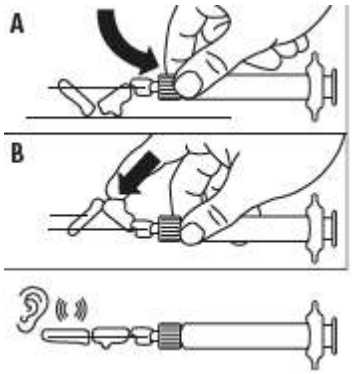
A. either by pressing the hinged section of the safety guard down onto a rigid surface, e.g. table

B. or by pushing the hinge forward with your forefinger making sure always to keep all fingers behind the needle tip.

An audible “click” confirms the proper activation of the safety mechanism.

Note: Record injection site on patient’s record and **alternate monthly**.

Dispose of the vial and the syringe with needle immediately in a sharps container or other rigid closed disposal container.



4.3. Contraindications:

Hypersensitivity to the active substance octreotide 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 TEVA.

Hepatic function should be monitored during OCTREOTIDE TEVA therapy.

Cardiovascular related events:

Cases of bradycardia have been reported. Dose adjustment of medicines such as beta blockers, calcium channel blockers, or medicines to control fluid and electrolyte balance, may be necessary (see **section 4.5**).

Gallbladder and related events:

Cholelithiasis is a very common event during OCTREOTIDE TEVA 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 in the post-marketing

setting. Ultrasonic examination of the gallbladder before and at about 6-monthly intervals during OCTREOTIDE TEVA therapy is recommended.

Glucose metabolism:

Because of its inhibitory action on growth hormone, glucagon, and insulin release, OCTREOTIDE TEVA may affect glucose regulation. Post-prandial glucose tolerance may be impaired. As reported for patients treated with s.c. octreotide, 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 concomitant Type I diabetes mellitus, OCTREOTIDE TEVA is likely to affect glucose regulation, and insulin requirements may be reduced. In non-diabetics and type II diabetics with partially intact insulin reserves, octreotide s.c administration may result in increases in post-prandial hyperglycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

In patients with insulinomas, octreotide as contained in OCTREOTIDE TEVA, 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.

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 TEVA in patients who have a history of vitamin B12 deprivation.

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.

Mannitol:

Patients with the rare hereditary condition of mannitol intolerance should not use OCTREOTIDE TEVA.

4.5. Interaction with other medicines and other forms of interaction:

Dose adjustment of medicines such as beta blockers, calcium channel blockers, or medicines to control fluid and electrolyte balance may be necessary when OCTREOTIDE TEVA is administered concomitantly (see **section 4.4**).

Dose adjustments of insulin and antidiabetic medicines may be required when OCTREOTIDE TEVA is administered concomitantly (see **section 4.4**).

Octreotide as contained in OCTREOTIDE TEVA has been found to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

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

Limited published data indicate that somatostatin analogues might decrease the metabolic clearance of compounds known to be metabolised by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect,

other medicines mainly metabolised by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution.

Concomitant use of radiopharmaceuticals coupled to somatostatin analogues (peptide receptor radionuclide therapy (PRRT)) somatostatin and its analogues (e.g. octreotide) bind competitively to somatostatin receptors and may impair the efficacy of relevant radiopharmaceuticals (e.g. (177 Lu) oxodotreotide). Administration of OCTREOTIDE TEVA as a long-acting somatostatin analogue must therefore be interrupted 4 to 6 weeks before initiation of treatment with PRRT. If required, patients may be treated with short-acting somatostatin analogues up to 24 hours before administration of PRRT.

Treatment with OCTREOTIDE TEVA may be resumed within 4 to 24 hours after administration of PRRT, but must be interrupted once again 4 to 6 weeks before the radiopharmaceutical is next administered.

4.6. Fertility, pregnancy and lactation:

Women of childbearing potential / Contraception in males and females:

Female patients of childbearing potential should be advised to use adequate contraception during treatment with OCTREOTIDE TEVA.

Pregnancy:

Experience with OCTREOTIDE TEVA in pregnant women is limited. Avoid the use of OCTREOTIDE TEVA during pregnancy (see **section 4.4**) as safety in pregnancy has not been established.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Lactation:

Experience with OCTREOTIDE TEVA in nursing women is limited.

It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk. Patients should not breastfeed during OCTREOTIDE TEVA treatment.

Fertility:

It is not known whether OCTREOTIDE TEVA has an effect on human fertility. Late descent of the testes was found for male off springs of dams 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.

4.7. Effects on ability to drive and use machines:

OCTREOTIDE TEVA can cause dizziness, asthenia/fatigue, or headache and may have no or negligible effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. Patients should be advised to be cautious when driving or using machines if they experience dizziness, asthenia/fatigue, or headache during treatment with OCTREOTIDE TEVA.

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 frequently 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.

Table 1 Adverse drug reactions reported in clinical studies:

The following adverse drug reactions, listed in Table 1, have been accumulated from reports from clinical studies with octreotide:

Adverse medicine reactions (Table 1) are ranked under heading of frequency. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Table 1 Adverse drug reactions reported in clinical studies:

Endocrine disorders:	
Frequent	Hypothyroidism, thyroid disorder (e.g., decreased TSH, decreased total T4, and decreased free T4).
Metabolism and nutrition disorders:	
Frequent	Hyperglycaemia, hypoglycaemia, impaired glucose tolerance, anorexia.
Less frequent	Dehydration.
Nervous system disorders:	
Frequent	Headache, dizziness.
Cardiac disorders:	
Frequent	Bradycardia.
Less frequent	Tachycardia.
Respiratory, thoracic and mediastinal disorders:	
Frequent	Dyspnoea.

Gastrointestinal disorders:	
Frequent	Diarrhoea, abdominal pain, nausea, constipation, flatulence, dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces.
Hepato-biliary disorders:	
Frequent	Cholelithiasis, cholecystitis, biliary sludge, hyperbilirubinaemia.
Skin and subcutaneous tissue disorders:	
Frequent	Pruritus, rash, alopecia.
General disorders and administration site conditions:	
Frequent	Injection site reactions, asthenia.
Investigations:	
Frequent	Elevated transaminase levels.

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 medicine 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.

Hepato-biliary disorders:
Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice.
Cardiac disorders:
Dysrhythmias.
Investigations:
Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels.

Description of selected adverse events:

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. The incidence in the general population (aged 40 to 60 years) is about 5 to 20 %. Long-term exposure to OCTREOTIDE TEVA of patients with acromegaly or gastro-entero-pancreatic tumours suggests that treatment with OCTREOTIDE TEVA does not increase the incidence of gallstone formation, compared with s.c. treatment. 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:

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.

Hypersensitivity and anaphylactic reactions:

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

Injection site reactions:

Injection site related reactions including pain, redness, haemorrhage, pruritus, swelling or induration were commonly reported in patients receiving OCTREOTIDE TEVA; however, these events did not require any clinical intervention in the majority of the cases.

Metabolism and nutrition disorders:

Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide as in OCTREOTIDE TEVA has led to nutritional deficiency due to malabsorption.

Pancreatic enzymes:

Acute pancreatitis has been reported within the first hours or days of octreotide s.c. treatment and resolved on withdrawal of the medicine. 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 (i.v.) in patients with cirrhosis of the liver, and during treatment with OCTREOTIDE TEVA. This is reversible after discontinuation of treatment.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose:

The adverse events reported were hot flushes, dysrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly, and lactic acidosis.

The management of overdosage is symptomatic and supportive.

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 prolonged duration of action. It inhibits pathologically increased secretion of growth hormone (GH) and of peptides and serotonin produced within the gastro-entero-pancreatic (GEP) endocrine system.

Octreotide has been shown to inhibit:

- release of growth hormone (GH) stimulated by arginine, exercise- and insulin-induced hypoglycaemia,
- post-prandial 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).

Octreotide inhibits GH secretion preferentially over insulin.

In previously untreated acromegaly patients with GH-secreting pituitary adenoma, long-acting octreotide treatment resulted in a tumour volume reduction of > 20 % in a significant proportion (50 %) of patients.

5.2 Pharmacokinetic properties

Absorption:

After single intramuscular (i.m) injections of long-acting octreotide the serum octreotide concentration reaches an initial peak within 1 hour after administration, followed by a progressive decrease to a low undetectable octreotide level within 24 hours. After this peak on day 1, octreotide remains at sub-therapeutic levels in the majority of the patients for the following 7 days. Thereafter, octreotide concentrations increase again, and reach plateau concentrations at around day 14 and remain relatively constant during the following 3 to 4 weeks. The peak level during day 1 is lower than levels during the plateau phase, and no more than 0,5 % of the total medicine occurs during day 1. After about day 42, the octreotide concentration decreases slowly, concomitant with the terminal degradation phase of the polymer matrix of the dosage form.

In patients with acromegaly, mean plateau octreotide concentrations after single doses of 10 mg, 20 mg and 30 mg of octreotide amount to 358 ng/l, 926 ng/l, and 1 710 ng/l, respectively. Steady-state serum octreotide concentrations, reached after 3 injections at 4-week intervals, are higher by a factor of approximately 1,6 to 1,8 and amount to 1 557 ng/l, and 2 384 ng/l after multiple injections of 20 mg and 30 mg of octreotide, respectively.

No accumulation of octreotide beyond that expected from overlapping release profiles occurred over a duration of up to 28 monthly injections of octreotide.
The pharmacokinetic profile of octreotide after injection of octreotide reflects the release profile from the polymer matrix and its biodegradation.

Distribution:

Once released into the systemic circulation, octreotide distributes according to its known pharmacokinetic properties, as described for s.c. administration. The volume of distribution of octreotide at steady state is 0,27 l/kg and the total body clearance is 160 ml/min. Plasma protein binding amounts to 65 % and essentially no drug is bound to blood cells.

Linearity:

In patients with carcinoid tumours, the mean (and median) steady-state serum concentrations of octreotide after multiple injections of 10 mg, 20 mg, and 30 mg of octreotide given at 4-week intervals also increased linearly with dose and were 1 231 (894) ng/l, 2 620 (2270) ng/l, and 3 928 (3010) ng/l, respectively.

6. PHARMACEUTICAL PARTICULARS:

6.1. List of excipients:

Powder (microspheres)

D,L-Lactide/Glycolide copolymer 55/45

Mannitol

Suspension vehicle

Carmellose sodium

Mannitol

Poloxamer 188

Water for injections

6.2. Incompatibilities:

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3. Shelf life:

36 months.

The product must not be stored after reconstitution (must be used immediately).

6.4. Special precautions for storage:

Store at 2 °C to 8 °C (in a refrigerator). Do not freeze.

Store in the original package in order to protect from light.

OCTREOTIDE TEVA is a single dose vial and any unused portion must be discarded.

For storage conditions after reconstitution, refer to **section 6.3**.

6.5. Nature and contents of container:

OCTREOTIDE TEVA consist of 8 mL Type I internally siliconised, clear glass vial, with a grey rubber stopper and sealed with aluminium flip-off cap of different colour (dark blue, orange and red-granate flip-off caps are used for 10 mg, 20 mg and 30 mg strengths respectively).

Suspension vehicle*:*

Consists of 3 mL, internally siliconised, Type I, clear glass pre-fillable syringe with tip cap stoppered with a 9,25 mm, grey colour, bromobutyl plunger stopper. A plunger rod is attached at the back end of the plunger stopper.

Cardboard box containing (1-unit or 3-unit pack size):

One or three glass vials containing: microspheres for injection.

One or three glass prefilled syringe (containing the suspension vehicle).

Administration components (i.e., a vial adapter and a safety needle).

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product:

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

1st Floor, Building 3, Maxwell Office Park

Magwa Cresent West, Waterfall City

Midrand, Gauteng, South Africa

2090

8. REGISTRATION NUMBER:

OCTREOTIDE TEVA 10: 54/34/0425

OCTREOTIDE TEVA 20: 54/34/0426

OCTREOTIDE TEVA 30: 54/34/0427

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

02 March 2021

10. DATE OF REVISION OF TEXT:

15 March 2023