For the Use of a Registered Medical Practitioner Only

PRESCRIBING INFORMATION

OCTRIDE INJECTION 50 MCG/ML
OCTRIDE INJECTION 100 MCG/ML
(Octreotide Injection)

1. NAME OF THE MEDICINAL PRODUCT

OCTRIDE INJECTION 50 MCG/ML
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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OCTRIDE INJECTION 50 MCG/ML
Each mcg/ml contains
Octreotide Acetate eq. Octreotide ……0.050 mg/ml

OCTRIDE INJECTION 100 MCG/ML
Each mcg/ml contains
Octreotide Acetate eq. Octreotide ……0.100 mg/ml

3. PHARMACEUTICAL FORM

Solution for injection. The solution is clear and colourless.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Indicated for the 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. It is also indicated for acromegalic patients unfit or unwilling to undergo surgery or in the interim period or until radiotherapy becomes fully effective.

For the relief of symptoms associated with the gastro-entero-pancreatic (GEP) endocrine tumours:

- Carcinoid tumours with features of the carcinoid syndrome,
- VIPomas
- Glucagonomas.
- Gastrinomas/Zollinger-Ellison syndrome, usually in conjunction with proton pump inhibitors or H, antagonist therapy
- Insulinomas, for preoperative control of hypoglycaemia and for maintenance therapy

- GRFomas

The effect of octreotide is limited to the alleviation of signs and symptoms; it will not cure the underlying condition.

Prevention of complications following pancreatic surgery.

Emergency management to stop bleeding and to protect from rebleeding owing to gastrooesophageal varices in patients with cirrhosis. It is to be used in association with specific treatment such as endoscopic sclerotherapy.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Dose

Acromegaly: 0.05 – 0.1 mg by subcutaneous injection every 8 or 12 hours initially, then monthly adjustment in the light of circulating GH (target GH<2.5mg/ml; IGF-1 within the normal range), clinical response and tolerability. For most patients the optimum dose will be 0.3mg. A maximum dose of 1.5mg per day should not be exceeded. For patients on a stable dose of octreotide, assessment of GH should be made every 6 months. If no relevant reduction in GH levels and no improvement in clinical symptoms have been achieved within 3 months of starting treatment, therapy should be discontinued.

GEP endocrine tumours: 0.05mg once or twice daily by subcutaneous injection initially, gradually increasing to 0.1 to 0.2mg three times daily depending on tolerability and therapeutic effect (clinical response, levels of tumour produced hormones and in cases of carcinoid tumours, on the urinary excretion of 5-hydroxy indole acetic acid). Higher doses may be required in some cases. Maintenance dosage requires individual titration. In carcinoid tumours if there is no beneficial reponse within 1 week of treatment with octreotide at the maximum tolerated dose, therapy should not be continued.

Prevention of complications following pancreatic surgery: 0.1mg three times daily by subcutaneous injection for seven consecutive days, the first injection being administered at least one hour before the start of the operation.

Bleeding gastro-oesophageal varices: 0.025mg/hour, given as a continuous IV infusion for five days. Octreotide may be diluted with physiological saline. In cirrhotic patients with bleeding gastro oesophageal-varices, octreotide has been well tolerated at continous IV doses of upto 0.05mg/hour for five days.

Elderly: There is no evidence of reduced tolerability or altered dosagerequirements in elderly patients treated with octreotide.

Children: Experience with octreotide in children is very limited.

Hepatic impairment: In patients with liver cirrhosis, the half live of the drug may be increased, necessitating adjustment of the maintenance dose.

Renal impairment: Impaired renal function did not affect the total exposure (AUC) to octreotide administered as subcutaneous injection; therefore no dosage adjustment of octreotide is necessary. To reduce local discomfort, let the solution reach room temperature before injection and avoid multiple injections at short intervals at the same site.

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

If Octreotide injection needs to be given as an IV infusion, the contents of one 0.5mg ampoule should normally be dissolved in 60ml 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the drug or its components.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

As GH-secreting pituitary tumors may sometimes expand, causing serious complications (e.g., visual field defects), it is essential that all patients be carefully monitored. If evidence of tumor expansion appears, alternative procedures may be advisable. The therapeutic benefits of a reduction in growth hormone (GH) levels and normalization 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

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

Cardiovascular related events

Cases of bradycardia have been reported (frequency: common). Dose adjustments of

drugs such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary.

Gallbladder and related events

Cholelithiasis is a very common event during octreotide treatment and may be associated with cholecystitis and biliary duct. 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- to 12-month intervals during octreotide therapy is therefore recommended.

GEP endocrine tumors

During the treatment of GEP endocrine tumors, there may be rare instances of sudden escape from symptomatic control by octreotide, with rapid recurrence of severe symptoms.

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 hyperglycemia may be induced as a result of chronic administration. Hypoglycemia 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 prandial increases in glycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

Oesophageal varices

Since, following bleeding episodes from esophageal 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

There have been no reports of tumor formation at the injection sites in patients treated with Octreotide for up to 15 years

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.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance may be necessary when **Octride Injection** is administered concomitantly.

Dose adjustments of insulin and antidiabetic medicinal products may be required when **Octride Injection** is administered concomitantly.

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

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

Limited data suggest that somatostatin analogues might decrease the metabolic clearance of the 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 effects, other drugs mainly metabolised by CYP3A4 and which have a low therapeutic index should therefore be used with caution (e.g., terfenadine). Octreotide has been associated with an alteration in nutrient absorption, so it may have an effect on absorption of drugs administered orally.

4.6 FERTILITY, PREGNANCY AND LACTATION

Preqnancy:

There are no adequate and well-controlled studies in pregnant women. In the post-marketing experience data on a limited number of exposed pregnancies have been reported in patients with acromegaly, however, in half of the cases the pregnancy outcomes are unknown. In most of the cases with known outcome, normal newborns were reported but also several spontaneous abortions during the first trimester, and a few induced abortions. There were no cases of congenital anomalies or malformations due to octreotide usage in the cases that reported pregnancy outcomes. **Octride Injection** should only be prescribed to pregnant woman under compelling circumstances (see section WARNINGS AND PRECAUTIONS).

Lactation

It is unknown whether octreotide is transferred into human breast milk. Animal studies have shown transfer of octreotide into breast milk. Patients should not breast-feed during Octreotide treatment.

Fertility

It is not known whether octreotide has an effect on human fertility.

4.7 UNDESIRABLE EFFECTS

The main side effects are local and gastrointestinal.

Local reactions: It includes pain, a sensation of stinging, tingling or burning at the site of subcutaneous injection, with redness and swelling. They rarely last more than fifteen minutes. Local discomfort may be reduced by allowing the solution to reach room temperature before injection.

Body as a whole: Rarely hypersensitivity skin reactions, transient hair loss, isolated reports of anaphylactic reactions are observed.

Cardiovascular system: isolated cases of bradycardia have also been reported.

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

Heptobiliary: Prolonged use of Octreotide may results in gallstone formation & there have been isolated reports of biliary colic following the abrupt withdrawal of the drug in acromegalic patients in whom biliary sludge or gallstones had developed. There have been isolated reports of hepatic dysfunctions associated with octreotide administration. These consist of acute hepatitis, without cholestasis, where transaminase values have normalised on withdrawal of octreotide, or Slow development of hyperbilirubinaemia in association with elevation of alkaline phosphatase, gamma glutamyl transferase and, to a lesser extent, transaminases.

Pancreas: Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation. It may impair postprandial glucose tolerance and in some instances with chronic administration, a state of persistent hyperglycaemia may be induced. Hypoglycemia has also been observed. In rare instances acute pancreatitis has been reported and generally observed within the first hours or days of octreotide treatment and resolves on withdrawal of the drug. In addition, cholelithiasis induced pancreatitis has been reported in patients on long term octreotide therapy.

OVERDOSE

Doses of up to 2000mcg as subcutaneous injection three times a day for several months have been well tolerated. No life-threatening reactions have been reported after acute overdosage. The maximum single dose so far given to an adult has been 1 mg by intravenous bolus injection. The observed signs and symptoms were a brief drop in heart rate, facial flushing, abdominal cramps, diarrhoea, an empty feeling in the stomach and nausea, all of which resolved within twenty-four hours of drug administration. One patient has been reported to have received an accidental overdosage of octreotide by continuous infusion (250 micrograms per hour for forty-eight hours instead of 25 micrograms per hour). He experienced no side effects.

The management of overdosage is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: ATC code: H01CB02

Mechanism of Action

Octreotide is a synthetic octapeptide analogue of naturally occurring somatostatin with similar pharmacological effects, but with a longer duration of action. It inhibits pathologically increased secretion of growth hormone and of peptides and serotonin produced within the gastro-enteropancreatic endocrine system.

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

In normal healthy subjects octreotide is shown to inhibit the release of growth hormone stimulated by arginine, exercise and insulin-induced hypoglycemia; post-prandial release of insulin, glucagon, gastrin, other peptides of the gastroentero- pancreatic endocrine system; arginine-stimulated release of insulin and glucagon and thyrotropin releasing hormonestimulated release of thyroid stimulating hormone. Because of its diverse endocrine effects, octreotide modifies different clinical features in patients with tumours of the gastro-entero-pancreatic endocrine system. Its effects in the different tumour types are as follows:

Carcinoid tumours: Octreotide may improve symptoms, particularly flush and diarrhoea. In many cases there is a fall in plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid.

VIPomas: In most cases, octreotide alleviates the severe secretory diarrhoea typical of the condition, with consequent improvement in quality of life. This is accompanied by an improvement in associated electrolyte abnormalities, e.g., hypokalaemia, enabling enteral and parenteral fluid and electrolyte supplementation to be withdrawn. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas: Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect 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. It produces improvement of diarrhoea and hence weight gain in those patients that are affected. Although, the administration of octreotide often leads to an immediate reduction in plasma glucagon levels, it is generally not maintained over a prolonged period of administration despite continued symptomatic improvement.

Acromegaly: Octreotide lowers plasma levels of GH and/or IGF-1. In most patients, octreotide markedly reduces the clinical symptoms of the disease such as headache, skin and soft tissue swelling, hyperhidrosis, arthralgia and paraesthesia.

Insulinomas: Octreotide produces a fall in circulating insulin which may however be of short duration. In patients with operable tumours, octreotide may help to restore and maintain normoglycaemia preoperatively and in patients with inoperable tumours, benign or malignant, glycaemic control may be improved without concomitant sustained reduction in circulating insulin levels.

Gastrinomas/Zollinger-Ellison syndrome: Octreotide alone or in conjunction with proton pump inhibitors or H, blockers may reduce gastric acid hypersecretion and improve symptoms including diarrhoea. Other symptoms possibly due to peptide production by the tumour, e.g., flush, may also be relieved. Plasma gastrin levels fall in some patients.

GRFomas: Octreotide produces improvement in the features and symptoms of the resultant acromegaly that occurs with this rare tumour. This is probably due to inhibition of GH releasing factor (GRF) and GH secretion, and a reduction in pituitary enlargement may follow.

Acute variceal bleeding: Although the exact mechanism is not fully understood but it is postulated that octreotide reduces splanchnic blood flow through inhibition of vasoactive hormones (e.g., VIP, glucagon).

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, postoperative acute pancreatitis).

5.2 PHARMACOKINETICS PROPERTIES

Absorption

After subcutaneous injection octreotide is rapidly and completely absorbed with peak plasma concentrations reaching within 30 minutes. Plasma protein binding is about 65% and the amount bound to blood cells is negligible.

Distribution

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

Elimination

The elimination half life after subcutaneous administration is 100 minutes. After IV 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 subcutaneous injection. The elimination capacity may be reduced in patients with liver cirrhosis but not in patients with fatty liver disease.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Glacial acetic acid, sodium acetate trihydrate, sodium chloride, water for injection.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except for those mentioned in the dosage and administration section

6.3 SHELF-LIFE

24 Months

6.4 SPECIAL PRECATIONS FOR STORAGE

Store between 2^{o}C and 8 ^{o}C, protected from light.

6.5 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Not applicable

7. PRODUCT REGISTRATION HOLDER/MANUFACTURER

Product Registration Holder:
Ranbaxy (Malaysia) Sdn Bhd
Lot 23, Bakar Arang Industrial Estate,
08000 Sungai Petani, Kedah, Malaysia.

Manufacturer:
Sun Pharmaceutical Industries Ltd.
Halol-Baroda Highway, Halol – 389350 India

8. DATE OF REVISION

January 2025