Pediatric Use
Safety and efficacy of Octreotide Injection in the pediatric population have not been demonstrated.
No formal controlled clinical trials have been performed to evaluate the safety and effectiveness of Octreotide in pediatric under age 6 years. In post-marketing report, serious adverse events, including hypoxia, necrotizing enterocolitis, and death, have been reported with Octreotide use in children, most notably in children under 2 years of age. The relationship of these events to octreotide has not been established as the majority of these pediatric patients had serious underlying co-morbid conditions.

Geriatric Use
Clinical studies of Octreotide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSE
A limited number of accidental overdoses of octreotide acetate in adults 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 t.i.d.). Adverse events in some patients included arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, hepatomegaly, lactic acidosis, flushing, diarrhea, lethargy, weakness, and weight loss.

Octreotide acetate Injection given in intravenous boluses of 1 mg (1000 mcg) to healthy volunteers did not result in serious ill effects, nor did doses of 30 mg (30,000 mcg) given intravenously over 20 minutes and of 120 mg (120,000 mcg) given intravenously over 8 hours in research patients.

Storage: Store in a dry place at 2° to 8°C. Do not freeze. Protect from light.
Improper storage may be detrimental to the product.

Marketed by:

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For the use of a Registered Medical Practitioner or a Hospital or Laboratory only

Octreotide Acetate Injection 50 mcg/ml

OCTREOCAN 50 MCG INJ

For Deep Subcutaneous (Intradal) or Intravenous Use
1ml Ampoule

Composition :
Each ml contains :
Octreotide Acetate
Eq. to Octreotide 50 mcg
Water for Injection IP q.s.

DRUG DESCRIPTION

Octreotide acetate Injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in a buffered lactic acid solution for administration by deep subcutaneous (intradal) or intravenous injection. Octreotide acetate, known chemically as L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-[2-hydroxy-1-(hydroxymethyl)propyl], cyclic (2→7)-disulfide; [R-(R*, R*)] acetate salt, is a long-acting octapeptide with pharmacologic actions mimicking those of the natural hormone somatostatin.

The molecular weight of octreotide acetate is 1019.3 (free peptide, $C_{49}H_{66}N_{10}O_{10}S_2$) and its amino acid sequence is:

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol.

xCH3COOH where x = 1.4 to 2.5

CLINICAL PHARMACOLOGY

After subcutaneous injection, octreotide is absorbed rapidly and completely from the injection site. Peak concentrations of 5.2 ng/ml. (1000 mcg dose) were reached 0.4 hours after dosing. Using a specific radioimmunoassay, intravenous and subcutaneous doses were found to be bioequivalent. Peak concentrations and area under the curve values were dose proportional after intravenous single doses up to 200 mcg and subcutaneous single doses up to 500 mcg and after subcutaneous multiple doses up to 500 mcg t.i.d. (1500 mcg/day).

In healthy volunteers the distribution of octreotide from plasma was rapid (t½ = 0.2 h), the volume of distribution was estimated to be 13.6 L, and the total body clearance ranged from 7 L/hr to 10 L/hr.

The elimination of octreotide from plasma had an apparent half-life of 1.7 to 1.9 hours compared with 1-3 minutes with the natural hormone. The duration of action of octreotide acetate is variable but extends up to 12 hours depending upon the type of tumor. About 32% of the dose is excreted unchanged into the urine. In an elderly population, dose adjustments may be necessary due to a significant increase in the half-life (48%) and a significant decrease in the clearance (26%) of the drug.

In patients with acromegaly, the pharmacokinetics differ somewhat from those in healthy volunteers. A mean peak concentration of 2.8 ng/mL (1000 mcg dose) was reached in 0.7 hours after subcutaneous dosing. The volume of distribution (Vdss) was estimated to be 21.4–35.5 L and the total body clearance was increased to 18 L/h. The mean percent of the drug bound was 41.2%. The disposition and elimination half-lives were similar to normal.

In patients with renal impairment the elimination of octreotide from plasma was prolonged and total body clearance reduced. In mild renal impairment (CrCl 40-60 mL/min) octreotide t½ was 2.4 hours and total body clearance was 8.8 L/hr, in moderate impairment (CrCl 10-39 mL/min) it was 3.0 hours and total body clearance 7.51 hr, and in severely renally impaired patients not requiring dialysis (CrCl < 10 mL/min) it was 3.1 hours and total body clearance was 7.61 hr. In patients with severe renal failure requiring dialysis, total body clearance was reduced to about half that found in healthy subjects (from approximately 10 L/hr to 4.5 L/hr).

INDICATIONS

Acromegaly
Octreotide is indicated to reduce blood levels of growth hormone and IGF-1 (somatomedin C) in acromegaly patients who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses. The goal is to achieve normalization of growth hormone and IGF-1 (somatomedin C) levels. In patients with acromegaly, octreotide reduces growth hormone to within normal ranges in 50% of patients and reduces IGF-1 (somatomedin C) to within normal ranges in 50%-60% of patients. Since the effects of pituitary irradiation may not become maximal for several years, adjunctive therapy with octreotide to reduce blood levels of growth hormone and IGF-1 (somatomedin C) offers potential benefit before the effects of irradiation are manifested.

Improvement in clinical signs and symptoms or reductions in tumor size or rate of growth were not shown in clinical trials performed with octreotide; these trials were not optimally designed to detect such effects.

Carcinoid Tumors
Octreotide is indicated for the symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.

Octreotide studies were not designed to show an effect on the size, rate of growth or development of metastases.

Vasoactive Intestinal Peptide Tumors (VIPomas)
Octreotide is indicated for the treatment of the profuse watery diarrhea associated with VIP-secreting tumors. Octreotide studies were not designed to show an effect on the size, rate of growth or development of metastases.

DOSAGE AND ADMINISTRATION

Octreotide may be administered subcutaneously or intravenously. Subcutaneous injection is the usual route of administration of octreotide for control of symptoms. Pain with subcutaneous administration may be reduced by using the smallest volume that will deliver the desired dose. Multiple subcutaneous injections at the same site within short periods of time should be avoided. Sites should be rotated in a systematic manner.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **Do not use if particulates and/or discoloration are observed.** Proper sterile technique should be used in the preparation of parenteral admixtures to minimize the possibility of microbial contamination. **Octreotide is not compatible in Total Parenteral Nutrition (TPN) solutions because of the formation of a glycosyl octreotide conjugate which may decrease the efficacy of the product.**

Octreotide is stable in sterile isotonic saline solutions or sterile solutions of dextrose 5% in water for 24 hours. It may be diluted in volumes of 50-200 mL and infused intravenously over 15-30 minutes or administered by IV push over 3 minutes. In emergency situations (e.g., carcinoid crisis) it may be given by rapid bolus.

The initial dosage is usually 50 mcg administered twice or three times daily. Upward dose titration is frequently required. Dosage information for patients with specific tumors are as follows.

Acromegaly
Dosage may be initiated at 50 mcg t.i.d. Beginning with this low dose may permit adaptation to adverse gastrointestinal effects for patients who will require higher doses. IGF-1 (somatomedin C) levels every 2 weeks can be used to guide titration. Alternatively, multiple growth hormone levels at 0-8 hours after octreotide administration permit more rapid titration of dose. The goal is to achieve growth hormone levels less than 5 ng/mL or IGF-1 (somatomedin C) levels less than 1.9 U/mL in males and less than 2.2 U/mL in females. The dose most commonly found to be effective is 100 mcg t.i.d., but some patients require up to 500 mcg t.i.d. for maximum effectiveness. Doses greater than 500 mcg day seldom result in additional biochemical benefit, and if an increase in dose fails to provide additional benefit, the dose should be reduced. IGF-1 (somatomedin C) or growth hormone levels should be re-evaluated at 6-month intervals.

Octreotide should be withdrawn yearly for approximately 4 weeks from patients who have received irradiation to assess disease activity. If growth hormone or IGF-1 (somatomedin C) levels increase and signs and symptoms recur, octreotide therapy may be resumed.

Carcinoid Tumors
The suggested daily dosage of octreotide during the first 2 weeks of therapy ranges from 100-600 mcg/day in 2-4 divided doses (mean daily dosage is 300 mcg). In the clinical studies, the median daily maintenance dosage was approximately 450 mcg, but clinical and biochemical benefits were obtained in some patients with as little as 50 mcg, while others required doses up to 1300 mcg/day. However, experience with doses above 750 mcg/day is limited.

VIPomas
Daily dosages of 200-300 mcg in 2-4 divided doses are recommended during the initial 2 weeks of therapy (range: 150-750 mcg) to control symptoms of the disease. On an individual basis, dosage may be adjusted to achieve a therapeutic response, but usually doses above 450 mcg/day are not required.

SIDE EFFECTS

Gallbladder Abnormalities
Gallbladder abnormalities, especially stones and/or biliary sludge, frequently develop in patients on chronic octreotide therapy.

Cardiac
In acromegalics, sinus bradycardia (< 50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during therapy.

Gastrointestinal
Diarrhea, loose stools, nausea and abdominal discomfort were each seen in 34%-61% of acromegalic patients in U.S. studies although only 2-6% of the patients discontinued therapy due to these symptoms. These symptoms were seen in 5%-10% of patients with other disorders.

The frequency of these symptoms was not dose-related, but diarrhea and abdominal discomfort generally resolved more quickly in patients treated with 300 mcg/day than in those treated with 750 mcg/day. Vomiting, flatulence, abnormal stools, abdominal distention, and constipation were each seen in less than 10% of patients.

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

Hypo/Hyperglycemia
Hypoglycemia and hyperglycemia occurred in 3% and 16% of acromegalic patients, respectively, but only in about 1.5% of other patients. Symptoms of hypoglycemia were noted in approximately 2% of patients.

Hypothyroidism
In acromegalics, biochemical hypothyroidism alone occurred in 12% while goiter occurred in 6% during therapy. In patients without acromegaly, hypothyroidism has only been reported in several isolated patients and goiter has not been reported.

Other Adverse Events
Pain on injection was reported in 7.7%, headache in 6% and dizziness in 5%. Pancreatitis was also observed.

Other Adverse Events 1%-4%
Other events (relationship to drug not established), each observed in 1%-4% of patients, included fatigue, weakness, pruritus, joint pain, backache, urinary tract infection, cold symptoms. Ha symptoms, injection site hematoma, bruise, edema, flushing, blurred vision, pollakiuria, fat malabsorption, hair loss, visual disturbance and depression.

Other Adverse Events < 1%
Events reported in less than 1% of patients and for which relationship to drug is not established are listed:

Gastrointestinal: hepatitis, jaundice, increase in liver enzymes, GI bleeding, hemorrhoids, appendicitis, gastric/peptic ulcer.

Integumentary: rash, cellulitis, petechiae, urticaria, basal cell carcinoma.

Musculoskeletal: arthritis, joint effusion, muscle pain, Raynaud's phenomenon.

Cardiovascular: chest pain, shortness of breath, thrombophlebitis, ischemia, congestive heart failure, hypertension, hypotensive reaction, palpitations, orthostatic BP decrease, tachycardia.

CNS: anxiety, libido decrease, syncope, tremor, seizure, vertigo, Bell's Palsy, paresis, pituitary apoplexy, increased intracular pressure, amnesia, hearing loss, neuritis.

Respiratory: pneumonia, pulmonary nodule, status asthmaticus.

Endocrine: galactorrhea, hypoadrenalism, diabetes insipidus, gynecomastia, amenorrhea, polymenorrhea, oligomenorrhea, vaginitis.

Urogenital: nephrolithiasis, hematuria.

Hematologic: anemia, iron deficiency, epistaxis.

Miscellaneous: urticaria, allergic reaction, increased CK, weight loss.
Evaluation of 20 patients treated for at least 6 months has failed to demonstrate titers of antibodies exceeding background levels. However, antibody titers to octreotide were subsequently reported in three patients and resulted in prolonged duration of drug action in two patients. Anaphylactoid reactions, including anaphylactic shock, have been reported in several patients receiving octreotide.

DRUG INTERACTIONS

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments if these therapeutic agents.

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

WARNINGS

Single doses of Octreotide have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials (primarily patients with acromegaly or psoriasis), the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Octreotide for 12 months or longer were 52%. Less than 2% of patients treated with Octreotide for 1 month or less developed gallstones. The incidence of gallstones did not appear related to age, sex or dose. Like patients without gallbladder abnormalities, the majority of patients developing gallbladder abnormalities on ultrasound had gastrointestinal symptoms. The symptoms were not specific for gallbladder disease. A few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestasis, hepatitis, or pancreatitis during Octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Octreotide therapy and died.

PRECAUTIONS

General
Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon and growth hormone, which may result in hypoglycemia or hyperglycemia. Octreotide also suppresses secretion of thyroid-stimulating hormone, which may result in hypothyroidism. Cardiac conduction abnormalities have also occurred during treatment with Octreotide. However, the incidence of these adverse events during long-term therapy was determined vigorously only in acromegaly patients who, due to their underlying disease and/or the subsequent treatment they receive, are at an increased risk for the development of diabetes mellitus, hypothyroidism, and cardiovascular disease. Although the degree to which these abnormalities are related to Octreotide therapy is not clear, new abnormalities of glycemic control, thyroid function and ECG developed during Octreotide therapy as described below.

Risk of Pregnancy with Normalization of IGF-1 and GH
Although acromegaly may lead to infertility, there are reports of pregnancy in acromegalic women. In women with active acromegaly who have been unable to become pregnant, normalization of GH and IGF-1 may restore fertility. Female patients of childbearing potential should be advised to use adequate contraception during treatment with octreotide.

The hypoglycemia or hyperglycemia which occurs during Octreotide therapy is usually mild, but may result in overt diabetes mellitus or necessitate dose changes in insulin or other hypoglycemic agents. Hypoglycemia and hyperglycemia occurred on Octreotide in 3% and 16% of acromegalic patients, respectively. Severe hyperglycemia, subsequent pneumonia, and death following initiation of Octreotide therapy was reported in one patient with no history of hyperglycemia.

In acromegalic patients, 12% developed biochemical hypothyroidism only, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Octreotide. Baseline and periodic assessment of thyroid function (TSH, total and/or free T_4) is recommended during chronic therapy.

In acromegalics, bradycardia (< 50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias occurred in 9% of patients during Octreotide therapy. Other EKG changes observed included QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, and early R wave progression. These EKG changes are not uncommon in acromegalic patients. Dose adjustments in drugs such as beta-blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Octreotide therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge.

Several cases of pancreatitis have been reported in patients receiving Octreotide therapy.

Octreotide may alter absorption of dietary fats in some patients.

In patients with severe renal failure requiring dialysis, the half-life of Octreotide may be increased, necessitating adjustment of the maintenance dosage.

Depressed vitamin B_{12} levels and abnormal Schilling's tests have been observed in some patients receiving Octreotide therapy, and monitoring of vitamin B_{12} levels is recommended during chronic Octreotide therapy.

Pregnancy Category B
There are no adequate and well-controlled studies of Octreotide use in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest recommended human dose based on body surface area and revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether octreotide is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when octreotide is administered to a nursing woman.