Renavel

400mg & 800mg

Sevelamer HCL

film coated tablets

ریناویل گولیاں
(سیویلامر ایچ سی ایل)

Composition:

RENAVEL – 400 mg

Each film coated tablet contains:

Sevelamer hydrochloride 400mg

RENAVEL – 800 mg

Each film coated tablet contains:

Sevelamer hydrochloride 800mg

(Genome's Specs.)

Description:

The active ingredient in RENAVEL tablets is Sevelamer hydrochloride, a polymeric amine that binds phosphate and is meant for oral administration. Sevelamer hydrochloride is poly (allylamine hydrochloride) cross linked with epichlorohydrin in which forty percent of the amines are protonated. It is known chemically as poly (allylamine-co-N, N'-diallyl-1, 3-diamino-2-hydroxypropane) hydrochloride. Sevelamer hydrochloride is hydrophilic, but insoluble in water.

Clinical Pharmacology:

Pharmacodynamics:

Patients with end-stage renal disease (ESRD) retain phosphorus and can develop hyperphosphataemia. RENAVEL contains sevelamer hydrochloride, a non-absorbed phosphate binding poly(allylamine hydrochloride) polymer, free of metal and calcium. It contains multiple amines separated by one carbon from the polymer backbone. These amines become partially protonated in the Intestine and interact with phosphorus molecules through ionic and hydrogen bonding. By binding phosphorus in the dietary tract and decreasing absorption sevelamer hydrochloride lowers the phosphorus concentration in the serum.

When the product of serum calcium and phosphorus concentrations (Ca x P) exceeds 4.46 (mmol/L), there is an increased risk that ectopic calcification will occur. Hyperphosphataemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. An increase in parathyroid hormone (PTH) levels is characteristic of patients with chronic renal failure. Increased levels of PTH can lead to the bone disease osteitis fibrosa. A decrease in serum phosphorus may decrease serum PTH levels.

Treatment of hyperphosphosphatemia includes reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders

and removal of phosphate with dialysis. Sevelamer hydrochloride taken with meals has been shown to decrease serum phosphorus concentrations in patients with ESRD who are on hemodialysis. RENAVEL does not contain aluminum or other metals and does not cause aluminum intoxication.

In addition to effects on serum phosphate levels, sevelamer hydrochloride has been shown to bind bile acids in vitro and in vivo in experimental animal models. Binding of sevelamer hydrochloride with bile acids, result in lowering of LDL and total cholesterol levels.

Pharmacokinetics:

Studies using 14C- Sevelamer hydrochloride in 16 healthy male and female volunteers showed that sevelamer hydrochloride is not systemically absorbed. No absorption studies have been performed in patients with renal disease.

Indications:

RENAVEL is indicated for the control of hyperphosphataemia in patients with chronic kidney disease on dialysis.

Contraindications:

RENAVEL is contraindicated in patients with hypophosphataemia or bowel obstruction. RENAVEL is also contraindicated in patients known to be hypersensitive to sevelamer hydrochloride or any of the other components of the tablet.

Precautions:

The safety and efficacy of sevelamer hydrochloride has not been studied in patients with swallowing disorders, untreated or severe gastroparesis, and retention of gastric contents. Sevelamer hydrochloride should only be used in these patients following careful assessment of benefit and risks. Efficacy and safety of sevelamer hydrochloride has not been studied in patients with active inflammatory bowel disease, gastrointestinal motility disorders, abnormal or irregular bowel motion and patients with a history of major gastrointestinal surgery.Consequently, caution should be exercised when sevelamer hydrochloride is used in patients with these disorders. In very rare cases, intestinal obstruction and ileus/subileus have been observed in patients during treatment with sevelamer hydrochloride. Constipation may be a preceding symptom. Patients who are constipated should be monitored carefully while being treated with sevelamer hydrochloride. Sevelamer hydrochloride treatment should be reevaluated in patients who develop severe constipation or other severe gastrointestinal symptoms.

Sevelamer hydrochloride alone is not indicated for the control of hyperparathyroidism. In patients with secondary hyperparathyroidism sevelamer hydrochloride should be used within the context of a multiple therapeutic approach, which could include calcium supplements, 1,25 - dihydroxy Vitamin D3 or one of its analogues to lower the intact parathyroid hormone (PTH) levels.

Patients with renal insufficiency may develop hypocalcaemia or hypercalcaemia. Sevelamer hydrochloride does not contain calcium. Serum calcium levels should be monitored as is done in normal follow-up of a dialysis patient. Elemental calcium should be given as a supplement in case of hypocalcaemia.

Depending on diet intake and the nature of end stage renal failure, dialysis patients may develop low vitamin A, D, E and K levels. In preclinical studies, sevelamer hydrochloride at the equivalent of 6 -10 times the maximal human dose has been shown to reduce the absorption of vitamins D, E and K, and folic acid. Therefore, in patients not taking these vitamins, monitoring vitamin A, D and E levels and assessing vitamin K status through the measurement of thromboplastin time should be considered and the vitamins should be supplemented if necessary. Additional monitoring of vitamins and folic acid is recommended in patients receiving peritoneal dialysis, since in the clinical study, vitamin A, D, E and K levels were not measured in these patients. There is at present insufficient data to exclude the possibility of folate deficiency during long term sevelamer hydrochloride treatment.

Serum chloride may increase during sevelamer hydrochloride treatment as chloride may be exchanged for phosphorus in the intestinal lumen. Although no clinically significant serum chloride increase has been observed in the clinical studies, serum chloride should be monitored as is done in the routine follow-up of a dialysis patient.

Patients with chronic renal failure are predisposed to developing metabolic acidosis. Worsening of acidosis has been reported upon switching from other phosphate binders to sevelamer hydrochloride in a number of studies where lower bicarbonate levels in the sevelamer-treated patients compared to patients treated with calcium-based binders were observed. Closer monitoring of serum bicarbonate levels is therefore recommended.

Carcinogenicity/Mutagenicity:

Sevelamer hydrochloride was administered in the diet to rats and mice for two years. In mice and female rats, there was no increase in the incidence of tumours. In male rats, there was an increased incidence of transitional cell papillomas and transitional cell carcinomas in the urinary bladder at a dose of 3 g/kg/day, which is 10 times the maximum daily human dose (mg/kg basis) for a 50 kg person examined in clinical trials. These findings were considered likely to be secondary to increased serum and urinary calcium levels and inflammatory responses in the urinary bladder and their relevance to humans is unknown.

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In an in vitro mammalian cytogenetics test with metabolic activation, sevelamer hydrochloride caused a statistically significant increase in the number of structural chromosome aberrations. Sevelamer hydrochloride was not mutagenic in the Ames bacterial mutation assay. Based on the available evidence, sevelamer hydrochloride is considered unlikely to be genotoxic in vivo following oral administration.

Impairment of Fertility:

Sevelamer hydrochloride administered orally to male and female rats prior to and throughout mating, at doses up to 4.5 g/kg/day (15 times the maximum tested human dose on a mg/kg basis of a 50 kg person) did not alter mating or fertility.

Pregnancy & Lactation:

The safety of Sevelamer hydrochloride has not been established in pregnant or lactating women. In animal studies there was no evidence that sevelamer hydrochloride induced embryo-foetal toxicity. Sevelamer hydrochloridel should only be given to pregnant or lactating women if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and the foetus or infant.

Use in Children:

The safety and effectiveness of sevelamer hydrochloride in pediatric patients have not been established.

Instructions to Patients:

The contents of sevelamer hydrochloride expand in water thus tablets should be swallowed intact and should not be crushed, chewed or broken into pieces prior to administration.

Interactions:

Sevelamer hydrochloride was studied in human drug-drug interaction studies with digoxin, warfarin, enalapril, metoprolol, iron and ciprofloxacin. In interaction studies in healthy volunteers, sevelamer hydrochloride had no effect on the bioavailability of digoxin, warfarin, enalapril or metoprolol. However, the bioavailability of ciprofloxacin was decreased by approximately 50% when co-administered with sevelamer hydrochloride in a single dose study. Consequently, sevelamer hydrochloride should not be taken simultaneously with ciprofloxacin.

Sevelamer hydrochloride may affect the bioavailability of other medicinal products. When administering a medicinal product where a reduction in the bioavailability of that product could have a clinically significant effect on its safety or efficacy, the medicinal product should be administered at least one hour before or three hours after sevelamer hydrochloride, or the physician should consider monitoring blood levels.

Adverse Effects:

In parallel design studies involving 202 haemodialysis patients with treatment duration of 52 weeks and 97 peritoneal dialysis patients with treatment duration of 12 weeks, the most frequently occurring (=5% of patients) undesirable effects possibly or probably related to sevelamer hydrochloride were all in the gastrointestinal disorders system organ class. Data possibly or probably related to sevelamer hydrochloride from these studies (299 patients) and from uncontrolled clinical trials (384 patients) are **listed below:**

Gastrointestinal Disorders: Nausea, vomiting, abdominal pain, constipation, diarrhoea, dyspepsia, flatulence

Nervous system disorders: Headache
Vascular disorders: Hypotension, hypertension
General disorders: Pain
Skin and subcutaneous site conditions: Pruritis, Rash
Infections and infestations: Pharyngitis

Most of these events are commonly observed in patients Stage 5 Chronic Kidney Disease and are not necessarily attributable to sevelamer hydrochloride.

Dosage and Administration:

The recommended starting dose for patients not taking a phosphate binder is 800 to 1600 mg which can be administered as one to two RENAVEL 800 mg tablets or two to four 400 mg RENAVEL tablets with each meal based on serum phosphorus level. The below table provides recommended starting doses of RENAVEL for patients not taking a phosphate binder.

SERUM PHOSPHORUS	RENAVEL 800 mg	RENAVEL 400 mg
>5.5 and < 7.5mg/dl	1 tablet three times daily with food	2 tablets three times daily with food
≥7.5 and < 9.0 mg/dL	2 tablets three times daily with food	3 tablets three times daily with food
≥9.0 mg/dL	2 tablets three times daily with food	4 tablets three times daily with food

If Sevelamer hydrochloride is prescribed as an alternative phosphate binder, RENAVEL should be given in equivalent doses on a mg weight basis compared to the patient's previous calcium based phosphate binder. Serum phosphate levels should be closely monitored and the dose of RENAVEL adjusted accordingly with the goal of lowering serum phosphate to 1.76 mmol/l (5.5 mg/dl) or less. Serum phosphate should be tested every two to three weeks until a stable serum phosphate level is reached and on a regular basis thereafter.

Dose Titration for All Patients Taking Sevelamer.: Dosage should be adjusted based on the serum phosphorus concentration with a goal of lowering serum phosphorus to 5.5 mg/dL or less. The dose may be increased or decreased by one tablet per meal at two week intervals as necessary

Note: Patients should take RENAVEL with meals and adhere to their prescribed diets. The tablets must be swallowed whole and not chewed.

Over dosage:

Sevelamer hydrochloride has been given to normal healthy volunteers in doses of up to 14 grams per day for 8 days with no adverse effects. There are no reported overdoses of sevelamer hydrochloride in patients. Since Sevelamer hydrochloride is not absorbed, the risk of systemic toxicity is low.

Storage:

Store below 30°C. Protect from heat light & moisture.
Keep all medicines out of the reach of children.
Shelf Life: please refer to expiry date on blister pack /carton.

Presentation:

RENAVEL - 400/800mg is available in Aluminum blister pack of 3x 10 tablets.

دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
روشنی، نمی اور گرمی سے بچائیں۔
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

Manufactured by:
GENOME PHARMACEUTICALS (PVT.) LTD.
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Marketed by:
AMP
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