

PRODUCT MONOGRAPH

K-DUR

(Potassium Chloride) Sustained Release Tablets

1500 mg - 20 mmol (mEq)

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DATE OF PREPARATION:
March 2, 2011

Control #: 145173

NAME OF DRUG: K-DUR Tablets

Potassium Chloride 1500 mg - 20 mmol (mEq) K⁺ in a sustained release tablet.

THERAPEUTIC CLASSIFICATION: Potassium Supplement

ACTION

Potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal and smooth muscle and the maintenance of normal renal function. Potassium depletion may occur whenever the rate of potassium loss exceeds the rate of potassium intake. Such depletion usually develops slowly as a consequence of prolonged therapy with oral diuretics, primary or secondary hyperaldosteronism, diabetic ketoacidosis, severe diarrhea, or inadequate replacement of potassium in patients on prolonged parenteral nutrition. Potassium depletion due to these causes is usually accompanied by a concomitant deficiency of chloride and is manifested by hypokalemia and metabolic alkalosis.

K-DUR Tablets contain microcrystalloids which disperse upon disintegration of the tablet. The microcrystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of microcrystalloids and the controlled release of ion from them are intended to minimize the possibility of high local concentrations of potassium within the gastrointestinal tract.

INDICATIONS

1. For the treatment of patients with hypokalaemia with or without metabolic alkalosis in the treatment of digitalis intoxication, and for the treatment of patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure, selected patients with hypertension on long term diuretic therapy, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

CONTRAINDICATIONS

Potassium supplements are contraindicated in patients with hyperkalaemia since a further increase in potassium concentration in such patients can produce cardiac arrest. Hyperkalaemia may complicate any of the following conditions: acute and chronic renal failure, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of the potassium-sparing diuretic (e.g. spironolactone, triamterene), or other drugs causing hyperkalaemia such as captopril and enalapril.

Slow release potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. The administration of these preparations is contraindicated in such patients as well as in patients with dysphagia.

All solid dosage forms of potassium supplements are contraindicated in any patients in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS

Hyperkalaemia: In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalaemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalaemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment. Hyperkalaemia has the potential to promote quinidine toxicity.

Hypokalaemia: Should not be treated by the concomitant administration of potassium salts in a potassium-sparing diuretic (e.g. spironolactone, triamterene) or other drug causing hyperkalaemia such as captopril or enalapril since the simultaneous administration of these agents can produce severe hypokalaemia. Hypokalaemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt

such as potassium acedate, potassium bicarbonate or potassium citrate.

Gastrointestinal Lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths, in addition to upper gastrointestinal bleeding. These lesions are caused by a high localized concentration of potassium ions in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs. All oral potassium preparations should be prescribed with particular caution in patients with a history of peptic ulcer.

PRECAUTIONS

The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of the serum electrolytes, the electrocardiogram and the clinical status of the patient.

Potassium supplements should be used with caution in diseases associated with heart block since increased serum potassium may increase the degree of block.

Since anticholinergic agents have the potential to slow gastrointestinal motility, caution should be exercised when prescribing solid oral potassium preparations to patients concurrently receiving anticholinergic agents.

Usage During Pregnancy and in Nursing Mothers: Because of gastrointestinal hypomotility associated with pregnancy, solid oral potassium supplements should be given to pregnant women only if clearly needed.

ADVERSE REACTIONS

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best avoided by increasing fluid intake when possible,

taking the dose with meals or reducing the dose. Intestinal bleeding, ulceration, perforation and obstruction have been reported in patients treated with solid dosage forms of potassium salts and may occur with K-DUR (see Contraindication and Warnings).

One of the most severe adverse effects is hyperkalaemia (See Contraindications, Warnings and Overdosage). Skin rash has been reported rarely with potassium preparations.

OVERDOSAGE

Overdosage from therapeutic doses of solid oral potassium salts in persons with normal excretory mechanism rarely occurs; however, if excretory mechanisms are impaired, potentially fatal hyperkalaemia may occur. Acute (accidental or intentional) overdosage of solid oral potassium salts have resulted in severe and/or fatal hyperkalaemia.

Symptoms

Overdosage with potassium is characterized chiefly by cardiovascular, neuromuscular and gastrointestinal disturbances.

Cardiovascular: ECG changes, hypotension and shock, bundle-branch block, ventricular arrhythmias, ventricular fibrillation leading possibly to cardiac arrest.

Neuromuscular: paresthesia, areflexia, convulsions, flaccid paralysis of striated muscle leading possibly to respiratory paralysis.

Gastrointestinal: nausea, vomiting, diarrhea and abdominal cramps.

Hyperkalaemia: It is important to recognize that hyperkalaemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic change which include increased amplitude and peaking of the T-wave, and flattening or absence of P-wave. As hyperkalaemia worsens prolongation of the P-R interval, widening of the QRS complex with S-T segment depression and arrhythmias may develop.

Widening of the QRS complex is one of the most ominous signs and indicates the need for aggressive treatment.

Treatment

The plasma concentration and electrocardiogram must be monitored in every case of potassium overdosage, as well as serum electrolytes, BUN, glucose and arterial blood gases.

Electrocardiographic signs of hyperkalaemia (tall peaked T-waves, P-R prolongation, disappearance of P-wave, QRS widening, heart block) are indications for immediate treatment.

In severe hyperkalaemia (plasma potassium exceeded 8mEq/L or ECG abnormalities include absence of P-wave, presence of widened QRS complex or ventricular arrhythmia).

- Administer intravenously 300 to 500mL/h of 10% dextrose solution containing 10-20 units of insulin per 1000 mL.
- Correct acidosis, if present, with intravenous sodium bicarbonate (44 to 132 mEq per litre of glucose solution).
- Administer 10 to 30mL of 10% calcium gluconate i.v. over 1 to 5 minutes under continuous ECG monitoring.

Administer cation exchange resin by high retention enema. 30 to 50g sodium polystyrene sulfonate suspended in 100 ml warm aqueous sorbital solution should be kept in the sigmoid colon for several hours, if possible. The colon is then irrigated with non-sodium containing solution to remove the resin. Repeated enemas can be administered, or the resin given repeatedly by mouth to maintain a physiologic potassium concentration.

Haemodialysis or peritoneal dialysis may be of use, particularly in patients with renal failure.

In moderately severe hyperkalaemia (plasma potassium between 6.5 and 8 mEq/L or ECG peaking of T-wave):

- Administer intravenously 300 to 500 mL/h of 10% dextrose solution containing 10-20 units of insulin per 1000 mL.
- Correct acidosis, if present, with intravenous sodium bicarbonate (44 to 132 mEq/L of glucose solution).
- Correct hyponatremia and hypovolemia, if present.

Once the patient's cardiac state has been stabilized, in the case of a recent acute ingestion of K-DUR, consideration should be given to the evacuation of the stomach. When overdosage is the result of chronic therapeutic ingestion, K-DUR should be discontinued immediately as well as potassium containing foods and medications and also potassium sparing diuretics.

DOSAGE AND ADMINISTRATION

The usual dietary intake of potassium by the average adult is 40 to 80 mmol (mEq) (3000 to 6000 mg) per day.

Potassium depletion sufficient to cause hypokalaemia usually requires the loss of 200 or more mmol (mEq) (15000mg) of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mmol (mEq) (1500 mg) per day for the prevention of hypokalaemia to 40-100 mmol (mEq) (3000-7500 mg) per day or more for the treatment of potassium depletion.

<u>K-DUR Tablets</u>	<u>For Prevention</u>	<u>For Treatment</u>
20 mmol (mEq) (1500 mg)	1 tablet per day 20 mmol (mEq) (1500 mg)	2-5 tablets per day 40-100 mmol (mEq) (3000-7500 mg)

If more than one (1) K-DUR 20 mmol (mEq) (1500 mg) tablets is prescribed per day, the total daily dosage should be divided into two or more separate doses.

Tablets should be taken with a glass of water or other liquid.

Patients having difficulty swallowing whole tablets may try one of the following alternate methods of administration.

- a) Break the tablet in half, and take each half separately with a glass of water.
- b) Prepare an aqueous (water) suspension as follow:
 - 1. Place the whole tablet in approximately one-half glass of water (115 mL).
 - 2. Allow 2-3 minutes for the tablets to disintegrate.
 - 3. Stir for about half a minute after the tablet has disintegrated.
 - 4. Drink the entire contents of the glass immediately.
 - 5. Add another small quantity of water, stir and drink immediately.

Aqueous suspension of K-DUR tablets that are not taken immediately should be discarded. The use of other liquids for suspending K-DUR tablets is not recommended.

AVAILABILITY

K-DUR 20 mmol (mEq) (1500 mg) Sustained Release Tablets are available in bottles of 100. They are capsule-shaped, white to off-white mottled tablets imprinted "K-DUR 20" on one and scored on the other.

STORAGE CONDITIONS

Keep tightly closed. Store at controlled room temperature 15-30°C.

CHEMISTRY

Molecular Formula: KCl

Molecular weight: 74.55

Description: Potassium Chloride is a white, odorless, anhydrous powder with a saline taste. Each gram represents 13.41 mmol (mEq) of potassium.

PHARMACOLOGY

Potassium is of fundamental importance in the ionic exchange of cellular metabolism. It is the predominant cation of intracellular fluid in which it is present in a concentration of 155 mmol (mEq)/L. Plasma contains 3.8 to 5 mmol (mEq)/L

Potassium ion is the principal intracellular ion of most body tissues. Potassium ions are involved in a number of essential physiological processes, including the maintenance of intercellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle and the maintenance of normal renal function.

Potassium deficiency may cause vomiting, abdominal distention, paralytic ileus, acute muscular weakness, paralysis, parathesia, polydipsia and an inability to concentrate urine, hypotension, cardiac arrhythmias, and coma. Hypokalaemia may also increase the toxicity of digitalis and other cardiac glycosides.

Potassium chloride is readily absorbed from the gastrointestinal tract. Excretion is mainly in the urine and closely follows potassium intake.

CLINICAL STUDIES

K-DUR tablets are non-irritating and non-toxic to the gastrointestinal tract as demonstrated in the following studies:

I. Bioavailability Studies

Data from a single-dose, pilot bioavailability study demonstrated that the K-DUR 20 mmol (mEq) tablet had the same extent of absorption as a liquid potassium preparation. Furthermore, the release of potassium from the tablet provided urine potassium levels equivalent to three (3) doses of liquid potassium every six (6)

hours.

Twenty-three (23) patients completed a single-dose, open label, two-way crossover bioavailability study with the K-DUR 20 mmol (mEq) tablet and a liquid potassium preparation. The cumulative urine potassium elimination over 24 hours produced a similar profile for both the liquid KCl and the K-DUR 20 mmol (mEq) tablet. These data indicated that the amount of potassium absorbed over 24 hours from an 80 mmol (mEq) dose of K-DUR is equal to three doses of 26.7 mmol (mEq) of KCl Elixir (80 mmol (mEq)) dosed six hours apart. The mean time to peak of the potassium urinary excretion rate was 2.2 hours for the liquid and 5.5 hours after K-DUR 20 mmol (mEq) tablet. This result illustrates the sustained release characteristic of the K-DUR product.

II. Controlled Clinical Studies

A study performed in twelve (12) subjects comparing K-DUR 20 mmol (mEq) tablets and placebo, administered b.i.d., showed that both products were well tolerated by all subjects. No clinical symptom, sign or test indicated a risk to any subject or were considered positively drug related. Endoscopy results, performed pre-dose and post-dose indicated no evidence of erythema, submucosal hemorrhages or ulceration.

Another study compared K-DUR 20 mmol (mEq) tablets with Slow-K, Micro-K, Kaon Elixir and placebo in seventy-five (75) subjects at a dose of 80 mEq a day, along with 6 mg of glycopyrrolate per day. In this study no serious endoscopic lesions were found with K-DUR, and in fact except for placebo the test drug showed the least amount of gastrointestinal changes as compared to the other formulations. Overall, the safety of K-DUR was equal to or better than the comparative agents.

ANIMAL TOXICOLOGY

A five day gastrointestinal irritation study was conducted in miniature swine comparing the 20 mmol (mEq) K-DUR tablet to enteric coated KCl (Enseals), Slow-K, placebo and an untreated control group. K-DUR showed little potential for causing more lesions than placebo and less potential for causing lesions than the wax matrix or enteric coated

preparations.

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