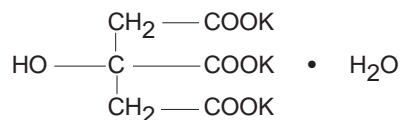


UROCIT[®]-K

Potassium Citrate

FULL PRESCRIBING INFORMATION

DESCRIPTION: Urocit[®]-K is a citrate salt of potassium. Its empirical formula is $K_3C_6H_5O_7 \cdot H_2O$, and its structural formula is:



Potassium citrate is a white granular powder that is soluble in water at 154 g/100 ml, almost insoluble in alcohol, and insoluble in organic solvents.

Urocit[®]-K is supplied as wax matrix tablets, containing 5 mEq (540 mg) potassium citrate and 10 mEq (1080 mg) potassium citrate each, for oral administration.

CLINICAL PHARMACOLOGY: When Urocit[®]-K is given orally, the metabolism of absorbed citrate produces an alkaline load. The induced alkaline load in turn increases urinary pH and raises urinary citrate by augmenting citrate clearance without measurably altering ultrafilterable serum citrate. Thus, Urocit[®]-K therapy appears to increase urinary citrate principally by modifying the renal handling of citrate, rather than by increasing the filtered load of citrate. The increased filtered load of citrate may play some role, however, as in small comparisons of oral citrate and oral bicarbonate, citrate had a greater effect on urinary citrate.

In addition to raising urinary pH and citrate, Urocit[®]-K increases urinary potassium by approximately the amount contained in the medication. In some patients, Urocit[®]-K causes a transient reduction in urinary calcium.

The changes induced by Urocit[®]-K produce a urine that is less conducive to the crystallization of stone-forming salts (calcium oxalate, calcium phosphate and uric acid). Increased citrate in the urine, by complexing with calcium, decreases calcium ion activity and thus the saturation of calcium oxalate. Citrate also inhibits the spontaneous nucleation of calcium oxalate and calcium phosphate (brushite).

The increase in urinary pH also decreases calcium ion activity by increasing calcium complexation to dissociated anions. The rise in urinary pH also increases the ionization of uric acid to more soluble urate ion.

Urocit[®]-K therapy does not alter the urinary saturation of calcium phosphate, since the effect of increased citrate complexation of calcium is opposed by the rise in pH-dependent dissociation of phosphate. Calcium phosphate stones are more stable in alkaline urine.

In the setting of normal renal function, the rise in urinary citrate following a single dose begins by the first hour and lasts for 12 hours. With multiple doses the rise in citrate excretion reaches its peak by the third day and averts the normally wide circadian fluctuation in urinary citrate, thus maintaining urinary citrate at a higher, more constant level throughout the day. When the treatment is withdrawn, urinary citrate begins to decline toward the pre-treatment level on the first day.

The rise in citrate excretion is directly dependent on the Urocit[®]-K dosage. Following long-term treatment, Urocit[®]-K at a dosage of 60 mEq/day raises urinary citrate by approximately 400 mg/day and increases urinary pH by approximately 0.7 units.

In patients with severe renal tubular acidosis or chronic diarrheal syndrome where urinary citrate may be very low (<100 mg/day), Urocit[®]-K may be relatively ineffective in raising urinary citrate. A higher dose of Urocit[®]-K may

therefore be required to produce a satisfactory citraturic response. In patients with renal tubular acidosis in whom urinary pH may be high, Urocit[®]-K produces a relatively small rise in urinary pH.

INDICATIONS AND USAGE: Potassium citrate is indicated for the management of renal tubular acidosis (RTA) with calcium stones, hypocitraturic calcium oxalate nephrolithiasis of any etiology, and uric acid lithiasis with or without calcium stones.

CONTRAINDICATIONS: Urocit[®]-K is contraindicated in patients with hyperkalemia (or who have conditions predisposing them to hyperkalemia), as a further rise in serum potassium concentration may produce cardiac arrest. Such conditions include: chronic renal failure, uncontrolled diabetes mellitus, acute dehydration, strenuous physical exercise in unconditioned individuals, adrenal insufficiency, extensive tissue breakdown, or the administration of a potassium-sparing agent (such as triamterene, spironolactone or amiloride).

Urocit[®]-K is contraindicated in patients in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract, such as those suffering from delayed gastric emptying, esophageal compression, intestinal obstruction or stricture or those taking anticholinergic medication. Because of its ulcerogenic potential, Urocit[®]-K should not be given to patients with peptic ulcer disease.

Urocit[®]-K is contraindicated in patients with active urinary tract infection (with either urea-splitting or other organisms, in association with either calcium or struvite stones). The ability of Urocit[®]-K to increase urinary citrate may be attenuated by bacterial enzymatic degradation of citrate. Moreover, the rise in urinary pH resulting from Urocit[®]-K therapy might promote further bacterial growth.

Urocit[®]-K is contraindicated in patients with renal insufficiency (glomerular filtration rate of less than 0.7 ml/kg/min), because of the danger of soft tissue calcification and increased risk for the development of hyperkalemia.

WARNINGS: HYPERKALEMIA: In patients with impaired mechanisms for excreting potassium, Urocit[®]-K administration can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of Urocit[®]-K in patients with chronic renal failure, or any other condition which impairs potassium excretion such as severe myocardial damage or heart failure, should be avoided.

INTERACTION WITH POTASSIUM-SPARING DIURETICS: Concomitant administration of Urocit[®]-K and a potassium-sparing diuretic (such as triamterene, spironolactone or amiloride) should be avoided, since the simultaneous administration of these agents can produce severe hyperkalemia.

GASTROINTESTINAL LESIONS: Because of reports of upper gastrointestinal mucosal lesions following administration of potassium chloride (wax-matrix), an endoscopic examination of the upper gastrointestinal mucosa was performed in 30 normal volunteers after they had taken glycopyrrolate 2 mg. p.o. t.i.d., Urocit[®]-K 95 mEq/day, wax-matrix potassium chloride 96 mEq/day or wax matrix placebo, in thrice daily schedule in the fasting state for one week. Urocit[®]-K and the wax-matrix formulation of potassium chloride were indistinguishable but both were significantly more irritating than the wax-matrix placebo. In a subsequent similar study, lesions were less severe when glycopyrrolate was omitted.

Solid dosage forms of potassium chloride have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high local concentration of potassium ions in the region of

the dissolving tablets, which injured the bowel. In addition, perhaps because wax-matrix preparations are not enteric-coated and release some of their potassium content in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The frequency of gastrointestinal lesions with wax-matrix potassium chloride products is estimated at one per 100,000 patient-years. Experience with Urocit®-K is limited, but a similar frequency of gastrointestinal lesions should be anticipated.

If there is severe vomiting, abdominal pain or gastro-intestinal bleeding, Urocit®-K should be discontinued immediately and the possibility of bowel perforation or obstruction investigated.

PRECAUTIONS: INFORMATION FOR PATIENTS:

Physicians should consider reminding the patient of the following:

To take each dose without crushing, chewing or sucking the tablet.

To take this medicine only as directed. This is especially important if the patient is also taking both diuretics and digitalis preparations.

To check with physician if there is trouble swallowing tablets or if the tablet seems to stick in the throat.

To check with the doctor at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

LABORATORY TESTS: Regular serum potassium determinations are recommended. Careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease or acidosis.

DRUG INTERACTIONS: POTASSIUM-SPARING DIURETICS: See WARNINGS section.

DRUGS THAT SLOW GASTROINTESTINAL TRANSIT TIME (such as anticholinergics) can be expected to increase the gastrointestinal irritation produced by potassium salts. (See CONTRAINDICATIONS section).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term carcinogenicity studies in animals have not been performed.

PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with Urocit®-K. It is also not known whether Urocit®-K can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Urocit®-K should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS: The normal potassium ion content of human milk is about 13 mEq/l. It is not known if Urocit®-K has an effect on this content. Caution should be exercised when Urocit®-K is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Some patients may develop minor gastrointestinal complaints during Urocit®-K therapy, such as abdominal discomfort, vomiting, diarrhea, loose bowel movements or nausea. These symptoms are due to the irritation of the gastrointestinal tract, and may be alleviated by taking the dose with meals or snack, or by reducing the dosage. Patients may find intact matrices in feces (See also CONTRAINDICATIONS, WARNINGS).

OVERDOSAGE: The administration of potassium salts to persons without predisposing conditions for hyperkalemia (see CONTRAINDICATIONS) rarely causes serious hyperkalemia at recommended dosages. It is important to recognize that hyperkalemia is usually asymptomatic and may be

manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-wave, loss of P-wave, depression of S-T segment and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following: (1) elimination of potassium-rich foods, medications containing potassium, and of potassium-sparing diuretics, (2) intravenous administration of 300-500 ml/hr of 10% dextrose solution containing 10-20 units of insulin/1000 ml, (3) correction of acidosis, if present, with intravenous sodium bicarbonate, and (4) use of exchange resins, hemodialysis or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

DOSAGE AND ADMINISTRATION: Treatment with Urocit®-K should be added to a regimen that limits salt intake (avoidance of foods with high salt content and of added salt at the table) and encourages high fluid intake (urine volume should be at least two liters per day). The objective of treatment with Urocit®-K is to provide Urocit®-K in sufficient dosage to restore normal urinary citrate (greater than 320 mg/day and as close to the normal mean of 640 mg/day as possible), and to increase urinary pH to a level of 6.0 to 7.0.

In patients with severe hypocitraturia (urinary citrate of less than 150 mg/day), therapy should be initiated at a dosage of 60 mEq/day (20 mEq three times/day or 15 mEq four times/day with meals or within 30 minutes after meals or bedtime snack). In patients with mild-moderate hypocitraturia (>150 mg/day), Urocit®-K should be initiated at a dosage of 30 mEq/day (10 mEq three times/day with meals). Twenty-four hour urinary citrate and/or urinary pH measurements should be used to determine the adequacy of the initial dosage and to evaluate the effectiveness of any dosage change. In addition, urinary citrate and/or pH should be measured every four months.

Doses of Urocit®-K greater than 100 mEq/day have not been studied and should be avoided.

Serum electrolytes (sodium, potassium, chloride and carbon dioxide), serum creatinine, and complete blood count should be monitored every four months. Treatment should be discontinued if there is hyperkalemia, a significant rise in serum creatinine, or a significant fall in blood hematocrit or hemoglobin.

HOW SUPPLIED: Urocit®-K is available for oral administration in tablet form in the following sizes: (NDC 0178-0600-01) 5 mEq potassium citrate and (NDC 0178-0610-01) 10 mEq potassium citrate, packaged in bottles of 100 each. Urocit®-K 5 mEq tablets are uncoated, modified ball-shaped, and tan to yellowish in color. Each 5 mEq tablet is debossed MPC 600 on one side and blank on the other side. Urocit®-K 10 mEq tablets are uncoated, elliptical-shaped, and tan to yellowish in color. Each 10 mEq tablet is debossed with 610 on one side and MISSION on the other side.

Store in a tight container.

Rx only.

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