PRODUCT MONOGRAPH

UROCIT®-K

(Potassium Citrate Extended-Release Tablets, USP)

Renal Stone treatment in patients with
hypocitraturia or uric acid lithiasis

Mission Pharmacal Company
10999 IH 10 West, Suite 1000
San Antonio, TX 78230
USA

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Potassium Citrate Extended-Release Tablets, USP

THERAPEUTIC CLASSIFICATION

Renal Stone treatment in patients with hypocitraturia or uric acid lithiasis.

ACTIONS

UROCIT®-K (Potassium citrate Extended-Release Tablets, USP) is an oral preparation of potassium citrate which is imbedded in wax matrix to insure slow release. The main physiological response to potassium citrate treatment is a rise in urinary citrate and urinary pH, largely a consequence of the alkali load, rather than the appearance in urine of administered citrate.

The dependence of citrate excretion on potassium citrate dose varies among individuals. Except in patients with severe renal tubular acidosis or chronic diarrheal syndrome (ileitis, intestinal by-pass surgery, colitis) where a larger dose may be required, urinary citrate may usually be kept within normal limits during **UROCIT®-K** treatment at a dosage of 20 mEq three times/day. In patients taking thiazides, potassium citrate not only prevents the development of hypokalemia but increases citrate excretion.

Potassium citrate therapy also reduces urinary saturation of calcium oxalate due to increased citrate complexation of calcium and reduced calcium ion activity. It does not alter the saturation of calcium phosphate, since the effect of increased citrate complexation of calcium is opposed by a rise in pH-dependent dissociation of phosphate.

The propensity for the crystallization of both calcium salts (oxalate and phosphate) is reduced, oweing to the inhibitor activity of citrate (or its complexes).

Finally, the solubility of uric acid is increased, because of the rise in urinary pH.

INDICATIONS AND CLINICAL USE

UROCIT®-K (Potassium Citrate Extended-Release Tablets, USP) 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 (Potassium Citrate Extended-Release Tablets, USP) is contraindicated in:

1. 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.

2. Patients with active urinary tract infection (with 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.

3. 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, adynamia episodica hereditaria, extensive tissue breakdown as in severe burns, or the administration of a potassium sparing agent (such as trimaterene, spironolactone or amiloride).

4. 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, dysphagia, esophageal compression e.g. enlarged left atrium, intestinal obstruction or stricture, or those taking anticholinergic medication.

5. Patients with peptic ulcer disease because of its ulcerogenic potential.

Interactions with Potassium-sparing Diuretics

Concomitant administration of **UROCIT®-K** and a potassium-sparing diuretic (such as trimaterene, spironolactone or amiloride) should be avoided, since the simultaneous administrations of these agents can produce severe hyperkalemia.

WARNINGS

Hyperkalemia

In patients with impaired mechanisms for excreting potassium, **UROCIT®-K** (Potassium Citrate Extended-Release Tablets, USP) 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.

Gastrointestinal Lesions

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 injures 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 1/100,000 patient years. Experience with **UROCIT®-K** is limited, but similar frequency of gastrointestinal lesions should be anticipated. If there is severe vomiting, abdominal pain or gastrointestinal bleeding, **UROCIT®-K** should be discontinued immediately and the possibility of bowel perforation or obstruction investigated.

PRECAUTIONS

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.

Heart Disease

UROCIT®-K (Potassium citrate Extended-Release Tablets, USP) should be used with caution in diseases associated with heart block since increased serum potassium may increase the degree of block.

Drug Interactions

1. Potassium-sparing Diuretics-Concomitant administration of **UROCIT®-K** (e.g. spironolactone, trimaterene or amiloride) and potassium-sparing diuretics can produce severe hyperkalemia and is contraindicated (see CONTRAINDICATIONS section).

2. **UROCIT®-K** should be used with caution in patients receiving drugs known to have a potential for hyperkalemia such as ACE inhibitors (e.g. Captopril, Enalapril), NSAID's (e.g. indomethacin), beta-blockers, heparin, and digoxin.

3. Drugs that slow gastrointestinal transit time (e.g. anticholinergic drugs) can be expected to increase the gastrointestinal irritation produced by potassium salts (see CONTRAINDICATIONS section).

Pregnancy

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 reproductive capacity. **UROCIT®-K** should be given to a pregnant woman only if clearly needed. As well, because of gastrointestinal hypomotility associated with pregnancy, **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.

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 the physician if they have 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.

ADVERSE REACTIONS

Some patients may develop minor gastrointestinal complaints during **UROCIT®-K** (Potassium Citrate, Extended-Release Tablets, USP) therapy, such as abdominal discomfort, flatulence, 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 snacks, or by reducing the dosage. Patients may find intact matrices in feces.

One of the most severe adverse effects from oral potassium salts is hyperkalemia (see WARNINGS). There have also been warnings of esophageal and gastrointestinal obstruction, bleeding ulcerations or perforation from wax-matrix potassium preparations. (See CONTRAINDICATIONS and WARNINGS sections).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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, arreflexia, convulsions, flaccid paralysis of striated muscle leading possibly to respiratory paralysis.

Gastrointestinal: Nausea, vomiting, diarrhea and abdominal cramps.

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 which include increased amplitude and peaking of the T-wave, and flattening or absence of P-wave. As hyperkalemia worsens prolongation of P-R interval, and widening of 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 hyperkalemia (tall peaked T-waves, P-R prolongation, disappearance of P-waves, QRS widening, heart block) are indications for immediate treatment.

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

- Administer intravenously 300 to 500 mL/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 mL.
- Correct acidosis, if present, with intravenous sodium bicarbonate (44 to 132 mEq per liter of glucose solution).
- Administer 10 - 30 mL 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 50 g sodium polystyrene sulfonate suspended in 100 mL warm aqueous sorbitol solution should be kept in the sigmoid colon for several hours, if possible. The colon is then irrigated with a non-sodium containing solution to remove the resin.

Repeated enemas can be administered, or the resin given repeatedly by month to maintain a physiologic potassium concentration.

Hemodialysis or peritoneal dialysis may be of use, particularly in patients with renal failure. In moderately severe hyperkalemia (plasma potassium between 6.5 and 8 mEq/L or ECG peaking of T-wave):

- Administer intravenously 300 to 500 mL/hr 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 **UROCIT®-K**, consideration should be given to the evacuation of the stomach. When overdosage is the result of chronic therapeutic ingestion, **UROCIT®-K** should be discontinued immediately as well as potassium containing foods and medications and also potassium-sparing diuretics.

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** (Potassium Citrate Extended-Release Tablets, USP) 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 p H 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.

AVAILABILITY

UROCIT®-K (Potassium Citrate Extended-Release Tablets, USP) is available for oral administration in tablet form (5 and 10 mEq potassium citrate/tablet) in bottles each containing 100 tablets. Non medicinal ingredients: carnauba wax and magnesium stearate. Store in a cool, dry place, in a tightly closed container, under controlled room temperature of 15 °C to 30 °C.

CONSUMER INFORMATION

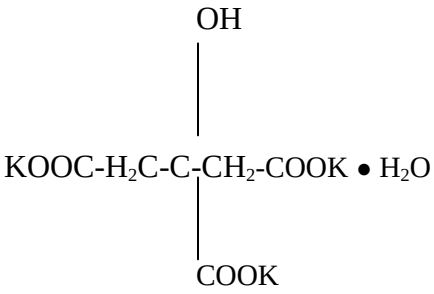
The consumer should take the following into consideration:

- Take each dose without crushing, chewing or sucking the tablet.
- Take this medicine only as directed. This is especially important if the consumer is also taking both diuretics and digitalis preparations.
- The consumer should check with physician if they have trouble swallowing tablets or if the tablet seems to stick in the throat.
- The consumer should check with physician at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

CHEMISTRY

Chemical Name: Potassium Citrate; 1,2,3-Propanetricarboxylic acid, 2-hydroxytripotassium salt, monohydrate

Structural Formula:



Molecular Formula: $K_3C_6O_7H_5 \bullet H_2O$

Molecular Weight: 324.41

PHARMACOLOGY

When **UROCIT®-K** (Potassium Citrate Extended-Release Tablets, USP) 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, potassium citrate 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, potassium citrate causes a transient reduction in urinary calcium.

The changes induced by potassium citrate produce 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.

Potassium citrate 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 pretreatment levels in the first day.

The rise in citrate excretion is directly dependent on the potassium citrate dosage. Following long-term treatment, potassium citrate 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), potassium citrate may be relatively ineffective in raising urinary citrate. A higher dose of potassium citrate may therefore be required to produce a satisfactory citraturic response. In patients with renal tubular acidosis in whom urinary pH may be high, potassium citrate produces a relatively small rise in urinary pH.

When **UROCIT®-K** is taken in a three-times-daily schedule, it causes a sustained rise in urinary citrate without a wide circadian fluctuation.

The physiological response (rise in urinary pH and citrate), occurred within one hour and lasted for 12 hours following a single dose of 20 mEq of **UROCIT®-K** (Potassium Citrate Extended-Release Tablets, USP). Following withdrawal of long-term treatment with potassium citrate for one week, urinary citrate decreased to pretreatment level. When given in twice-daily or thrice-daily schedule at a dosage of 60 mEq/day, the slow release preparation of potassium citrate virtually eliminated the circadian fluctuation in urinary citrate and maintained urinary citrate at a high constant level.

CLINICAL STUDIES

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 was matrix placebo, in thrice daily schedule in 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.

TOXICOLOGY

Long-term toxicity, carcinogenesis, mutagenesis, impairment of fertility studies in animals have not been performed with **UROCIT®-K** (Potassium Citrate Extended-Release Tablets, USP).

Carcinogenesis Mutagenesis Impairment of Fertility

Long term carcinogenicity studies in animals have not been performed.

REFERENCES

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