Potassium Citrate is a salt of potassium indicated for the management of:

- Renal tubular acidosis (RTA) with calcium stones
- Hypocitraturic calcium oxalate nephrolithiasis of any etiology
- Urinary acidosis with or without calcium stones

Dosage Forms and Strengths, Potassium Citrate 15 mEq (2.2, 2.3)

Dosage and Administration, Potassium Citrate 15 mEq (3)

**INDICATIONS AND USAGE**

- Renal tubular acidosis (RTA) with calcium stones (1.1)
- Hypocitraturic calcium oxalate nephrolithiasis of any etiology (1.2)
- Urinary acidosis with or without calcium stones (1.3)

**DOSEDOSAGE AND ADMINISTRATION**

Objective: 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.

- Severe hypocitraturia (urinary citrate < 150 mg/day): therapy should be initiated at 60 mg/day per meal, a dose of 30 mg three times per day, or 20 mg three times per day with meals or within three minutes after meals or bedtime snacks (2.2)
- MIM to moderate hypocitraturia (urinary citrate >150 mg/day): therapy should be initiated at 30 mg per day; a dose of 15 mg two times per day or 10 mg three times per day with meals or at least 30 minutes after meals or bedtime snacks (2.3)

**DOSE FORMS AND STRENGTHS**

Tablets: 15 mEq (3)

**CONTRAINDICATIONS**

- Patients with hyperkalemia (or who have conditions predisposing them to hyperkalemia). Such conditions include chronic renal failure, uncontrolled diabetes mellitus, acute dehydration, strenuous physical exercise in unconditioned individuals, adrenal insufficiency, extensive tissue breakdown (4)
- Patients for 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 (4)
- Patients with peptic ulcer disease (4)
- Patients with active urinary tract infection (4)
- Patients with renal insufficiency (glomerular filtration rate of less than 0.7 ml/min/1.73 m²) (4)

**WARNINGS AND PRECAUTIONS**

- Hyperkalemia: In patients with impaired mechanisms for excreting potassium, Potassium Citrate administration can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of Potassium Citrate in patients with chronic renal failure, or any other condition which impairs potassium excretion such as severe myoccardial damage or heart failure, should be avoided (5.1)
- Gastrointestinal lesions: if there is severe vomiting, abdominal pain or gastrointestinal bleeding, Potassium Citrate should be discontinued immediately and the possibility of bowel perforation or obstruction investigated (5.2)

**ADVERSE REACTIONS**

Some patients may develop minor gastrointestinal complaints such as abdominal discomfort, vomiting, diarrhea, loose bowel movements or nausea. These may be alleviated by taking the dose with meals or snacks or by reducing the dosage (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioPharma at 1-866-762-2365 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

The following drug interactions may occur with Potassium Citrate:

- Potassium-sparing diuretics: concomitant administration should be avoided since the simultaneous administration of these agents can produce severe hyperkalemia (7.1)
- Drugs that slow gastrointestinal transit time: These agents (such as anticholinergic) can be expected to increase the gastrointestinal irritation produced by potassium salts (7.2)

**USE IN SPECIFIC POPULATIONS**

- Pregnant women: Pregnancy Category C; animal reproduction studies have not been conducted. It is not known whether Potassium Citrate can cause fetal harm when administered to a pregnant woman or can affect reproduction capability. Potassium Citrate should be given to a pregnant woman only if clearly needed (8.1)
- Nursing mothers: The normal potassium ion content of human milk is about 13 mEq/L. It is not known if Potassium Citrate has an effect on this content. Potassium Citrate should be given to a woman who is breastfeeding only if clearly needed (8.3)
- Pediatric Use: Safety and effectiveness in children have not been established (8.4)

**FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE

1.1 Renal tubular acidosis (RTA) with calcium stones

1.2 Hypocitraturic calcium oxalate nephrolithiasis of any etiology

1.3 Urice acid lithiasis with or without calcium stones

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

2.2 Severe Hypocitraturia

2.3 Mild to Moderate Hypocitraturia

3 DOSAGE FORMS AND STRENGTHS

- 15 mEq tablets are uncoated, tan to yellowish in color, modified rectangle shaped, with M15 debossed on one side and blank on the other

4 CONTRAINDICATIONS

Potassium Citrate 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).
- 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.
- In patients with peptic ulcer disease because of its ulcerogenic potential.
- In patients with active urinary tract infection (with either ueria-splitting or other organisms, in association with either calcium or struvite stones). The ability of Potassium Citrate to increase urinary citrate may be attenuated by bacterial enzymatic degradation of citrate. Moreover, the rise in urinary pH resulting from Potassium Citrate therapy may lead to further bacterial growth.
- In patients with renal insufficiency (glomerular filtration rate of less than 0.7 ml/min/1.73 m²), because of the danger of soft tissue calcification and increased risk for the development of hyperkalemia.

5 WARNINGS AND PRECAUTIONS

5.1 Hyperkalemia

In patients with impaired mechanisms for excreting potassium, Potassium Citrate administration can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of Potassium Citrate in patients with chronic renal failure, or any other condition which impairs potassium excretion such as severe myoccardial damage or heart failure, should be avoided. Closely monitor for signs of hyperkalemia with periodic blood tests and ECGs.

5.2 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 glycocholate 2 mg p.o. t.i.d., Potassium Citrate 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. Potassium Citrate 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 glycocholate was omitted.

Solid dosage forms of potassium chlorides 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 may irritate 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 Potassium Citrate is limited, but a similar frequency of gastrointestinal lesions should be anticipated.

If there is severe vomiting, abdominal pain or gastrointestinal bleeding, Potassium Citrate should be discontinued immediately and the possibility of bowel perforation or obstruction investigated.

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

Some patients may develop minor gastrointestinal complaints such as abdominal discomfort, vomiting, diarrhea, loose bowel movements or nausea. These may be alleviated by taking the dose with meals or snacks, or by reducing the dosage (6.1)

7 DRUG INTERACTIONS

7.1 Potential Effects of Potassium Citrate on Other Drugs

Patients should be informed that concomitant administration of Potassium Citrate 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.

7.2 Potential Effects of Other Drugs on Potassium Citrate

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Nursing Mothers

8.3 Pediatric Use

8.4 Pediatric Use

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2010
10 OVERDOSAGE

Treatment of Overdosage: The administration of potassium salts to persons without predisposing conditions for hyperkalemia rarely causes serious hyperkalemia if given in usual therapeutic doses. Excess administration may be asymptomatic and may be manifested only by an increased serum potassium concentration and characteristically 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. Patients should be closely monitored for arrhythmias and electrolyte changes. 2. Elimination of medications containing potassium and of agents with potassium-sparing properties such as potassium–sparing diuretics, ARBs, ACE inhibitors, NSAIIDs, certain nutritional supplements and many others. 3. Elimination of foods containing high levels of potassium such as almonds, apricots, bananas, beets (lima, pinto, white), cantaloupe, carrot juice (canned), figs, grapefruit juice, halibut, milk, oat bran, potato (with skin), salmon, spinach, tuna and many others. 4. Intravenous sodium bicarbonate. 7. Hemodialysis or peritoneal dialysis. 8. Exchange transfuses may be used. However, this measure alone is not sufficient for the acute treatment of hyperkalemia.

Lowering potassium levels too rapidly in patients taking digitals can produce digitals toxicity.

11 DESCRIPTION

Potassium Citrate is a citrate salt of potassium. Its empirical formula is K₃C₆H₅O₇ • H₂O, and it has the following chemical structure:

\[
\text{CH}_3\text{COOK} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COOH} + \text{K}_3\text{C}_6\text{H}_5\text{O}_7
\]

Potassium Citrate yellowish to tan, oral waf- maties tablets, contain 15 mEq (1620 mg) potassium citrate each. Inactive ingredients include carnauba wax and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

When Potassium Citrate is given orally, the metabolism of absorbed citrate produces an alkaline load. The induced alkaline load is turn increases urinary pH and raises urinary citrate by augmenting citrate clearance without measurably altering urine pH. 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, Potassium Citrate increases urinary potassium by approximately the amount contained in the medication. 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 (nucleation).

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 the 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 peak by the third day and lasts 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 Potassium Citrate dosage. Following long-term treatment, Potassium Citrate at a dosage of 60 mEq/day raises urinary citrate by approximately 400 mEq/day and increases urinary pH by approximately 0.7 units.

In patients with severe renal tubular acidosis or chronic diuretic 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.

14 CLINICAL STUDIES

The pilotel Potassium Citrate trials were non-randomized and non-placebo controlled clinical study of five men and four women with calcium oxalate/calcium phosphate nephrolithiasis and documented incomplete distal renal tubular acidosis was examined. The main inclusion criterion was a history of stone passage or surgical removal of stones during the 3 years prior to initiation of Potassium Citrate therapy. All patients began alkali treatment with 60-80 mEq Potassium Citrate daily in 3 or 4 divided doses. Throughout treatment, patients were instructed to stay on a sodium limited diet (100 mEq/day) and to reduce oxalate intake (limited intake of nuts, dark rauqhage, chocolate and tea). A moderate calcium restriction (400-600 mg/day) was imposed on patients with hypercalcemia.

X-rays of the urinary tract, available in all patients, were reviewed to determine presence of pre-existing stones, appearance of new stones, or change in the number of stones.

Potassium Citrate therapy was associated with inhibition of new stone formation in patients with distal tubular acidosis. Three of the nine patients continued to pass stones during the trial treatment phase. While it is likely that these patients had pre-existing stones during therapy, the most conservative assumption is that the passed stones were newly formed. Using this assumption, the stone-passage reduction rate was 67%. All patients had a reduced stone formation rate. Over the first 2 years of treatment, the on-treatment stone formation rate was reduced from 13±2.7 to 1±2.8 per year.

14.2 Hypocitraturic calcium oxalate nephrolithiasis of any etiology

Eighty-nine patients with hypocitraturic calcium nephrolithiasis were recruited into the study. Forty-six patients had hypocitraturia and calcium stones, 8 patients had uric acid stones, and 3 patients had hyperuricosuria. Potassium Citrate therapy was given in a non-randomized, non-placebo controlled clinical study. Four groups of patients were treated with Potassium Citrate: Group 1 was comprised of 19 patients, 10 with renal tubular acidosis and 9 with chronic diuretic syndrome. Group 2 was comprised of 37 patients, 5 with uric acid stones alone, 6 with uric acid lithiasis and calcium stones, 3 with type 1 absorptive hypercalciuria, 9 with type 2 absorptive hypercalciuria and 14 with hyperuricosuria. Group 3 was comprised of 15 patients with history of relapse on other therapy and Group 4 was comprised of 18 patients, 9 with type 1 absorptive hypercalciuria and calcium stones, 1 with type 2 absorptive hypercalciuria and calcium stones, 2 with hyperuricosuric calcium oxate nephrolithiasis, 4 with uric acid lithiasis accompanied by calcium stones and 2 with hypouricosuria and hyperuricosuria accompanied by calcium stones. The dose of Potassium Citrate ranged from 30 to 100 mEq/day per day, and usually was 20 mEq administered orally 3 times daily. Patients were followed in an outpatient setting every 4 months during treatment and were studied over a period of 1 to 4.33 years. A three-year retrospective pre-study history for stone passage or removal was obtained and corroborated by medical records. Concomitant therapy (with thiazide or allopurinol) was allowed if patients had hypercalciuria, hyperuricosuria or hyperuricosuria. Group 2 was treated with Potassium Citrate alone.

In all groups, treatment that included Potassium Citrate was associated with a sustained increase in urinary citrate excretion from subnormal values to normal values (400 to 700 mg/day), and a sustained increase in urinary pH from 5.6-6.0 to approximately 6.5. The stone formation rate was reduced in all groups as shown in Table 1.

Table 1. Effect of Potassium Citrate With Calcium Oxalate Nephrolithiasis.

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>On Treatment</th>
<th>Remission*</th>
<th>Any Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n=19)</td>
<td>12 ± 0.9</td>
<td>0.9 ± 1.3</td>
<td>58%</td>
<td>95%</td>
</tr>
<tr>
<td>II (n=37)</td>
<td>1.2 ± 2</td>
<td>0.4 ± 1.5</td>
<td>89%</td>
<td>97%</td>
</tr>
<tr>
<td>III (n=15)</td>
<td>4.2 ± 1.7</td>
<td>0.7 ± 0.2</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>IV (n=18)</td>
<td>3.4 ± 0.8</td>
<td>0.5 ± 0.2</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Total (n=89)</td>
<td>4.3 ± 1.5</td>
<td>0.6 ± 0.2</td>
<td>98%</td>
<td>98%</td>
</tr>
</tbody>
</table>

* Remission defined as “the percentage of patients remaining free of newly formed stones during treatment”.

14.3 Uric acid lithiasis with or without calcium stones

A long-term non-randomized, non-placebo controlled clinical trial with eighteen adult patients with uric acid lithiasis participated in the study. Six patients formed only uric acid stones, and the remaining 12 patients formed mixed stones containing both acidic and calcium or formed both uric and calcium stones (without calcium salts) and calcium stones (without uric acid) on separate occasions.

Eleven of the 18 patients received Potassium Citrate alone. Six of the 7 other patients also received allopurinol for hyperuricosuria with gouty arthritis, symptomatic hyperuricosuria, or hyperuricosuria. One patient also received hydroxyurea alone because of unclassified hyperuricosuria. The main inclusion criterion was a history of stone passage or surgical removal of stones during the 3 years prior to initiation of Potassium Citrate therapy. All patients received potassium citrate at a dosage of 30-80 mEq/day in three-to-four divided doses and were followed every four months for up to 5 years.

While on Potassium Citrate treatment, urinary pH rose significantly from a low value of 5.3 ± 0.3 to within normal limits (6.2 to 6.5). Urinary citrate which was low before treatment rose to the high normal range and only one stone was formed in the entire group of 18 patients.

15 REFERENCES