5.1 Hyperkalemia

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 (5.1).

- Gastrointestinal lesions: if there is severe vomiting, abdominal pain or 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 gastrointestinal bleeding, Urocit-K should be discontinued immediately and the possibility of bowel perforation or obstruction investigated (5.2).

7.1 Potential Effects of Potassium Citrate on Other Drugs

- Renin-Angiotensin-Aldosterone System Inhibitors
- Nonsteroidal Anti-inflammatory drugs (NSAIDs)
- Pregnancy
- Nursing Mothers
- Pediatric Use

8. OVERDOSAGE

10. DESCRIPTION

14. CLINICAL STUDIES

14.1 Renal Tubular Acidosis (RTA) with Calcium Stones

14.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

14.3 Uric Acid Lithiasis with or without Calcium Stones

16. HOW SUPPLIED/STORAGE AND HANDLING

17. PATIENT COUNSELING INFORMATION

17.1 Administration of Drug

*Sections or subsections omitted from the full prescribing information are not listed

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 Uric Acid Lithiasis with or without Calcium Stones

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

2.2 Severe Hypertrophia

5.1 Hyperkalemia

5.2 Gastrointestinal Lesions

5.3 Mild to Moderate Hypocitraturia

5.4 Female Reproductive Function

5.5 Male Reproductive Function

5.6 Irritation Produced by Potassium Salts

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Potential Effects of Potassium Citrate on Other Drugs

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 Geriatric Use

8.5 Renal Impairment

8.6 Hepatic Impairment

8.7 Pregnancy/Lactation

8.8 Children

8.9 Carboxyhemoglobin Levels

8.10 Effects on Laboratory Tests

9 DRUG INTERACTIONS

11 CLINICAL PHARMACOLOGY

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Clinical Pharmacology

14.1 Renal Tubular Acidosis (RTA) with Calcium Stones

14.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

14.3 Uric Acid Lithiasis with or without Calcium Stones

16. HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Administration of Drug

*Sections or subsections omitted from the full prescribing information are not listed

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 Uric Acid Lithiasis with or without Calcium Stones

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

2.2 Severe Hypertrophia

5.1 Hyperkalemia

5.2 Gastrointestinal Lesions

5.3 Mild to Moderate Hypocitraturia

5.4 Female Reproductive Function

5.5 Male Reproductive Function

5.6 Irritation Produced by Potassium Salts

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Potential Effects of Potassium Citrate on Other Drugs

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 Geriatric Use

8.5 Renal Impairment

8.6 Hepatic Impairment

8.7 Pregnancy/Lactation

8.8 Children

8.9 Carboxyhemoglobin Levels

8.10 Effects on Laboratory Tests

9 DRUG INTERACTIONS

11 CLINICAL PHARMACOLOGY

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Clinical Pharmacology

14.1 Renal Tubular Acidosis (RTA) with Calcium Stones

14.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

14.3 Uric Acid Lithiasis with or without Calcium Stones

16. HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Administration of Drug

*Sections or subsections omitted from the full prescribing information are not listed

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 Uric Acid Lithiasis with or without Calcium Stones

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

2.2 Severe Hypertrophia

5.1 Hyperkalemia

5.2 Gastrointestinal Lesions

5.3 Mild to Moderate Hypocitraturia

5.4 Female Reproductive Function

5.5 Male Reproductive Function

5.6 Irritation Produced by Potassium Salts

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Potential Effects of Potassium Citrate on Other Drugs

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 Geriatric Use

8.5 Renal Impairment

8.6 Hepatic Impairment

8.7 Pregnancy/Lactation

8.8 Children

8.9 Carboxyhemoglobin Levels

8.10 Effects on Laboratory Tests

9 DRUG INTERACTIONS

11 CLINICAL PHARMACOLOGY

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Clinical Pharmacology

14.1 Renal Tubular Acidosis (RTA) with Calcium Stones

14.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

14.3 Uric Acid Lithiasis with or without Calcium Stones

16. HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Administration of Drug

*Sections or subsections omitted from the full prescribing information are not listed

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 Uric Acid Lithiasis with or without Calcium Stones

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

2.2 Severe Hypertrophia

5.1 Hyperkalemia

5.2 Gastrointestinal Lesions

5.3 Mild to Moderate Hypocitraturia

5.4 Female Reproductive Function

5.5 Male Reproductive Function

5.6 Irritation Produced by Potassium Salts

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Potential Effects of Potassium Citrate on Other Drugs

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 Geriatric Use

8.5 Renal Impairment

8.6 Hepatic Impairment

8.7 Pregnancy/Lactation

8.8 Children

8.9 Carboxyhemoglobin Levels

8.10 Effects on Laboratory Tests

9 DRUG INTERACTIONS

11 CLINICAL PHARMACOLOGY

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Clinical Pharmacology

14.1 Renal Tubular Acidosis (RTA) with Calcium Stones

14.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

14.3 Uric Acid Lithiasis with or without Calcium Stones

16. HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Administration of Drug

*Sections or subsections omitted from the full prescribing information are not listed

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 Uric Acid Lithiasis with or without Calcium Stones

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

2.2 Severe Hypertrophia

5.1 Hyperkalemia

5.2 Gastrointestinal Lesions

5.3 Mild to Moderate Hypocitraturia

5.4 Female Reproductive Function

5.5 Male Reproductive Function

5.6 Irritation Produced by Potassium Salts

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Potential Effects of Potassium Citrate on Other Drugs

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 Geriatric Use

8.5 Renal Impairment

8.6 Hepatic Impairment

8.7 Pregnancy/Lactation

8.8 Children

8.9 Carboxyhemoglobin Levels

8.10 Effects on Laboratory Tests

9 DRUG INTERACTIONS

11 CLINICAL PHARMACOLOGY

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Clinical Pharmacology

14.1 Renal Tubular Acidosis (RTA) with Calcium Stones

14.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

14.3 Uric Acid Lithiasis with or without Calcium Stones

16. HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Administration of Drug

*Sections or subsections omitted from the full prescribing information are not listed
7.3 Renin-Angiotensin-Aldosterone System Inhibitors
Drugs that inhibit the renin-angiotensin-aldosterone system (RAAS) including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), spironolactone, eplerenone, or aldosterone produce potassium retention by inhibiting aldosterone production. Closely monitor potassium in patients receiving concomitant RAAS therapy.

7.4 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
NSAIDs may produce potassium retention by reducing renal synthesis of prostaglandin E and impairing the renin-angiotensin system. Closely monitor potassium in patients on concomitant NSAIDs.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Animal reproduction studies have not been conducted. 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.

8.3 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. Urocit-K should be given to a woman who is breastfeeding only if clearly needed.

8.4 Pediatric Use
Safety and effectiveness in children have not been established.

10 OVERDOSAGE
Treatment of Overdosage: The administration of potassium salts to persons without predisposing conditions for hyperkalemia rarely causes serious hyperkalemia at recommended dosages. It is important to remember 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. 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, NSAIDs, certain nutritional supplements and many others.
3. Elimination of foods containing high levels of potassium such as almonds, apricots, bananas, beans (lima, pinto, white), cantaloupe, carrot juice (canned), figs, grapefruit juice, halibut, milk, oat bran, potatoes with skin, salmon, spinach, tuna and many others.
4. Intravenous calcium gluconate if the patient is at no risk or low risk of developing digitalis toxicity. 5. Intravenous administration of intravenous calcium gluconate if the patient is at no risk or low risk of developing digitalis toxicity.

11 DESCRIPTION
Urocit-K is a citrate salt of potassium. Its empirical formula is K$_2$H$_3$O$_4$. It has the following chemical structure:

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
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 ultrafiltrable 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 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 (brushtite).

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.

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 widely normal 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 0.2 units.

In patients with severe renal tubular acidosis or chronic diarrheal syndrome where urinary citrate may be very low (<100 mEq/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.

14 CLINICAL STUDIES
The pivotal Urocit-K trials were non-randomized and non-placebo controlled where dietary management may have changed coincidentally with pharmacological treatment. Therefore, the results as presented in the following sections may oversate the effectiveness of the product.

14.1 Renal Tubular Acidosis (RTA) with Calcium Stones
The effect of oral potassium citrate therapy in a non-randomized, non-placebo controlled clinical study of five men and four women with distal renal tubular acidosis 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 5 years prior to initiation of potassium citrate therapy. All patients began alkali treatment with 60-80 mEq potassium citrate daily and urine citrate ranged from 30 to 100 mEq per day, and usually was 20 mEq per day.

While on potassium citrate treatment, urinary pH rises 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.

14.2 Urocit-K Yellow tablets are uncoated, tan to yellowish in color, carved “06” and impressed “Urocit-K 15 mEq” on one side and “URK537R0122” on the other, supplied in bottles as:

30-300 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.

16 HOW SUPPLIED/STORAGE AND HANDLING
Urocit-K 5 mEq tablets are uncoated, tan to yellowish in color, elliptical shaped, with 610 debossed on one side and MIS6 on the other, supplied in bottles as:

All patients began alkali treatment with 60-80 mEq potassium citrate daily and urine citrate ranged from 30 to 100 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.

17 PATIENT COUNSELING INFORMATION
17.1 Administration of Drug
Tell patients to take each dose without crushing, chewing or sucking the tablet.

Tell patients to take this medicine only as directed. This is especially important if the patient is also taking diuretics and diuretics preparations.

Tell patients to check with the doctor if there is trouble swallowing tablets or if the tablet seems to stick in the throat.

Tell patients to take this medicine at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

Tell patients that their doctor will perform regular blood tests and electrocardiograms to ensure safety.

Table 1. Effect of Urocit-K in Patients 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 ± 3</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 ± 7</td>
<td>0.7 ± 2</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>IV (n=18)</td>
<td>3.4 ± 8</td>
<td>0.5 ± 2</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Total (n=89)</td>
<td>4.3 ± 15</td>
<td>0.6 ± 2</td>
<td>80%</td>
<td>98%</td>
</tr>
</tbody>
</table>

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