MyCare Solutions™

PRESCRIPTION AND SERVICE REQUEST FORM

BioComp Pharma®

Complete entire form and **fax** to **210-581-1385**

For support **call 844-849-3636**
M-F 9 am – 6 pm (ET)

REQUESTED SERVICES:

☐ Insurance Benefit Investigation & Support ☐ Copay ☐ Alternative Coverage & Support Options

1. PATIENT INFORMATION

First Name _____ MI _____

Last Name _____

DOB ____/____/____ Gender ☐ M ☐ F ☐ Other

Address _____

City _____ State ____ Zip_____

Email _____

FOR PATIENTS UNDER 18 YEARS OF AGE:

Parent/Guardian Name _____
(First) (MI) (Last)

Cell (____)_____Other (____)_____

☐ Voicemail ☐ Text

Primary Language (if not English) _____

Caregiver Name (if applicable) _____

Caregiver Phone (____)_____

2. PRESCRIPTION INFORMATION & PRESCRIBER CERTIFICATIONS

Previous medication(s) (most recent first) _____ Weight _____ ☐ kg / ☐ lb Date recorded ____/____/____

Known medication allergies _____

PRESCRIPTION REQUIRED FOR PATIENT SERVICES TO SEND PRESCRIPTION TO THE **SPECIALTY PHARMACY AND/OR FACTOR ACCESS**

Medication	ICD-10 Code	Dose / Frequency / Instructions	No. of Refills
☐ Tiopronin Delayed-Release 100mg	☐ E72.01 – Cystinuria ☐ N20.0 – Calculus of Kidney ☐ Other _____		
☐ Tiopronin Delayed-Release 300mg	☐ E72.01 – Cystinuria ☐ N20.0 – Calculus of Kidney ☐ Other _____		
☐ Potassium Citrate 10mEq	☐ E72.01 – Cystinuria ☐ N20.0 – Calculus of Kidney ☐ Other _____		

My signature certifies that the person named on this form is my patient; that the information provided on this application, to the best of my knowledge, is complete and accurate; and that therapy with Tiopronin and/or Potassium Citrate 10mEq is medically necessary.

I acknowledge that I have obtained authorization to release the patient's personal health information and the information on this form and any prescription to BioComp Pharma, Inc. (together with its parents and affiliates, "BioComp") and its third-party business partners, vendors, and other agents ("Agents") for the purpose of providing product support services and the BioComp MyCare Solutions™ Program ("the Programs"), including conducting a benefits investigation. I further certify that any service provided by BioComp on behalf of any patient is not made in exchange for any express or implied agreement or understanding that I would recommend, prescribe, or use any BioComp product or service for anyone, and my decision to prescribe Tiopronin and/or Potassium Citrate 10mEq was based solely on my determination of medical necessity. I understand that my information may be used by BioComp to manage and improve the Programs, to communicate with me about my experience with the Programs, and/or to send to me and/or patients materials relating to the Programs. With respect to any free product provided to the patient listed above, I understand that provision of the product is not contingent on any purchase obligations. I also understand that no claim for reimbursement will be submitted to Medicare, Medicaid, or any third-party payer for medication received free of charge under the Programs, or for related medical procedures and services; nor should the free product be sold, traded, or distributed for sale. I authorize BioComp and its Agents, including in-network specialty pharmacies, through the BioComp MyCare Solutions Program to forward this prescription electronically, by facsimile, or by mail to the relevant in-network pharmacy for the above-named patient. In addition, I certify and warrant that this request has been prepared exclusively by me or my office. I understand that BioComp MyCare Solutions Program may revise, change, or terminate any services in the Programs at any time without notice to me. I will notify the Programs and the dispensing pharmacy (if known to me) immediately if Tiopronin and/or Potassium Citrate 10mEq is no longer medically necessary for this patient's treatment or if my patient's insurance status changes. I authorize BioComp on behalf of me and my patient to (1) forward the above service request form and furnish any information on this form to the insurer of the above-named patient and (2) forward the above prescription, by fax or other modes of delivery, to dispensing pharmacy. I agree to assist in efforts to secure access to Tiopronin and/or Potassium Citrate 10mEq to my patient in the event of a coverage delay. **I also understand that, as the prescribing healthcare professional for such patient, I must also comply with any other requirements in my state, including but not limited to state-specific prescription requirements, such as e-prescribing, state-specific prescription form, fax language, etc., and non-compliance with state-specific requirements could result in outreach to me as the prescriber.**

OPTIONAL – ☐ **TEXT MESSAGING:** By providing your patient's email address or cell phone number, and checking this box, you certify that you have obtained the patient's consent to receive email and/or text messages (as applicable) related to enrolling into the BioComp MyCare Solutions Program, including notifying the patient that they have the right to opt out of future messages at any time, and, in the case of text messages, that their wireless service provider's message/data rates may apply and their consent is not required as a condition of purchasing any goods or services from BioComp or its affiliates.

SIGN & DATE

_____ _____
PRESCRIBER SIGNATURE **DATE**

CA, MA, NC & PR: interchange is mandated unless prescriber writes the words "NO SUBSTITUTION." ATTN: New York and Iowa providers, please submit electronic prescription.

Please see full Prescribing Information on pages 5-8

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3. PREFERRED SPECIALTY PHARMACY

Prescription to be sent to Specialty Pharmacy by ☐ Healthcare Provider ☐ Patient Services

Ship to ☐ Patient's home ☐ Prescriber's office

Indicate preferred Specialty Pharmacy

Name _____ Phone (_____) _____ Fax (_____) _____

4. INSURANCE INFORMATION

DISREGARD OR SKIP THIS SECTION IF ATTACHING COPIES (FRONT AND BACK) OF ALL AVAILABLE INSURANCE AND PRESCRIPTION CARDS

Primary Health Insurance Carrier _____ Policyholder Name (First/Last) _____

Insurance Phone _____ Employer of Policyholder _____

Policy ID # _____ Relationship to Patient _____

Group # _____

Secondary Health Insurance Carrier _____

Insurance Phone _____ Group # _____

Policy ID # _____ Policyholder Name (First/Last) _____

Prescription Drug Insurance (if different) _____

Insurance Phone _____ RxBIN # _____

Policy ID # _____ RxPCN # _____

Group # _____

5. PRESCRIBER INFORMATION

REQUIRED – SPECIALTY PHARMACY WILL NEED TO CONTACT THE PROVIDER PRIOR TO DISPENSING

Prescriber Name _____ Address _____

Prescriber Facility Name _____ City _____ State ____ Zip _____

Office Contact Name _____ Phone (____) _____ Fax (____) _____

Specialty _____ NPI _____ Tax ID _____

Office Contact Email _____ State License _____

Please see full Prescribing Information on pages 5-8

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BioComp Pharma

Complete entire form and **fax** to **210-581-1385**

For support **call 844-849-3636**
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6. AUTHORIZATION FOR RELEASE AND USE OF HEALTH INFORMATION

PATIENT – PLEASE READ THE FOLLOWING CAREFULLY, THEN DATE AND SIGN WHERE INDICATED.

By signing this Authorization to Release Health Information ("Authorization"), I authorize my healthcare providers (including my pharmacies), and my health plans and insurers (collectively, the "Parties") to disclose to BioComp Pharma Inc., MyCare Solutions™ Program, including its parents, affiliates, and its third party business partners, vendors, and other agents (collectively, "BioComp"), information about my disease, treatment, insurance coverage, and payment for my therapy (together with the information I have provided on this Enrollment Form and may provide in the future, "my Information") for the purposes of BioComp providing me with patient support services and sending me communications that I have agreed to receive elsewhere in this Enrollment Form.

The Parties and BioComp may use and disclose my Information for the purposes of providing certain support services that I agree to in this Enrollment Form, including, but not limited to: (1) determining if I am eligible to participate in the BioComp MyCare Solutions Program ("the Program"); (2) to operate, manage, administer and improve the Program; (3) to communicate with me about my experience with the Program; (4) to send materials relating to the Program; (5) investigating my health insurance coverage; and (6) contacting me for follow-up on any adverse event that I may disclose regarding a BioComp product. I further authorize BioComp to de-identify my health Information and use it in performing research, education, business analytics, marketing studies, and/or other commercial purposes, including linkage with other de-identified information that BioComp may receive from other sources.

I understand that once my Information has been disclosed to BioComp, federal privacy laws may no longer protect my Information from further disclosure, but that BioComp intends to use and disclose my Information only in accordance with this Authorization or as otherwise allowed by law. I understand that BioComp may provide my dispensing pharmacy with payment to obtain, use or disclose my Information. I understand that my personal health information may be used for communications between BioComp and me which may be considered marketing. Dispensing pharmacies may receive remuneration in exchange for disclosing my Information and/or for providing me with support services in connection with the Program. I may have certain rights under applicable data privacy laws regarding my Information, including the right to access my Information held by BioComp. For further information regarding these rights, please reference BioComp's Privacy Policy at www.biocomppharma.com. I understand that I may withdraw this Authorization by written notice to BioComp that will end further reliance on this Authorization (and my participation in the Program), but it will not affect any use or disclosure of my Information before my notice of withdrawal is received and processed by BioComp.

I understand that I may refuse to sign this Authorization and that a refusal to sign will not affect my ability to obtain medical care, insurance coverage, or access to health benefits, including access to therapy. Authorization expires 5 years from the date I sign this Authorization unless applicable law provides otherwise or until I withdraw (terminate) this Authorization before that time. I understand that I may withdraw this Authorization at any time by sending a written notice with my name, address, and phone number, to BioComp, ATTN: Compliance, 8000 Interstate Hwy 10 West, Suite 407, San Antonio, TX 78230, or by emailing compliance@tiopronin.com

REQUIRED – By signing below, I certify that I have read and understand the Authorization for Release and Use of Health Information and agree to its terms. I understand that I am entitled to a copy of this Authorization upon request.

SIGN & DATE

Printed name if signed by legal representative

Relationship to patient

7. PATIENT CERTIFICATIONS

PATIENT – PLEASE READ THE FOLLOWING CAREFULLY, THEN DATE AND SIGN WHERE INDICATED.

I attest that I have a valid prescription for Tiopronin delayed-release tablets and/or Potassium Citrate 10 mEq extended-release tablets, that I reside in the US or a US territory, and that I am being treated by a prescriber in the US or a US territory. If enrolling in the Copay Program (defined below), I attest that I have commercial insurance, and I further attest that I will not use a state or federally funded health insurance program such as Medicare (including Medicare Part D), Medicaid, Medigap, VA, DoD, TRICARE®, or similar federal or state pharmaceutical assistance programs to pay in part or in full for my Tiopronin prescription.

I authorize BioComp to provide me with various therapy support services for which I am eligible, which may include but are not limited to:

- Patient education and adherence support
- Insurance benefits investigation to assess eligibility for coverage and reimbursement (if requested)
- Coverage and financial assistance support (if requested)
- Other support services that may be added in the future, as well as any information or materials related to such support services

I acknowledge and understand that BioComp cannot provide me with medical advice, and I will direct all treatment-related questions to my healthcare professional.

CONTINUED ON PAGE 4

Please see full Prescribing Information on pages 5-8

7. PATIENT CERTIFICATIONS (CONTINUED)

I understand and agree that BioComp Pharma, Inc. ("BioComp") may contact me about such services and information by mail, email, telephone call, fax, or other means at the telephone numbers, email addresses, and mailing addresses that I provide. I understand a representative from BioComp may contact me for follow up on any adverse events or product complaints that I may report regarding a BioComp product. I understand that I do not have to enroll in the BioComp MyCare Solutions™ Program and that if I choose not to enroll, then I can still receive my medication as prescribed by my physician. I may opt out of the BioComp MyCare Solutions Program at any time by calling the Case Management team at 844-849-3636, emailing Compliance@tiopronin.com, or sending a written notice that includes my name, address, and phone number, to BioComp, ATTN: Compliance, 8000 Interstate Hwy 10 West, Suite 407, San Antonio, TX 78230. BioComp reserves the right to modify or terminate any or all support services and/or the BioComp MyCare Solutions Program at any time without notice.

If enrolling in the BioComp Copay Program* (the "Copay Program"), I understand that my copay card information will be sent to my designated dispensing pharmacy with my prescription, and any assistance with my applicable cost-sharing or copayment for Tiopronin and/or Potassium Citrate will be made in accordance with the Copay Program terms and conditions.

*Not valid if the patient is utilizing a state or federally funded health insurance program, such as Medicare (including Medicare Part D), Medicaid, Medigap, VA, DoD, TRICARE®, state pharmaceutical assistance program, etc., to pay in part or in full for the Tiopronin and/or Potassium Citrate prescription.

I also agree that BioComp may verify my eligibility for the BioComp MyCare Solutions Program, and I understand that such verification may include contacting me or my healthcare provider for additional information and/or reviewing additional financial, insurance, and/or medical information. I further understand that no free product may be submitted for reimbursement to any payer, including Medicare and Medicaid; and no free product may be sold, traded, or distributed for sale. If approved for the BioComp MyCare Solutions Program, I will not seek to have the value of any medication provided to me under such Program to be counted toward my true-out-of-pocket (TrOOP) cost for prescription drugs for my Medicare Part D Plan. In addition, I agree to notify BioComp immediately if my insurance status or my income changes. BioComp reserves the right to review assistance requests based on patient needs and to change Program guidelines or terminate all or any portion of the Program at any time without notification.

COMMUNICATIONS AND OUTREACH FROM A BIOCOMP COMMUNITY RELATIONS MEMBER

I agree that BioComp and its Agents (such as third-party business partners) can contact me by mail, email, fax and/or telephone, including calls and text messages (if consent is provided to receive text messages), and send me information about rare medical disorders and relevant BioComp products, promotions, services, and research studies, ask my opinion about such information and topics, including through market research and disease-related surveys, and share the information that I provide with one another to perform these activities, and to de-identify it for use in performing research, education, business analytics, marketing studies, and other commercial purposes. If I agree to receive text messages, I understand that text messaging rates may apply. I understand that my information will not be sold to any third party, but may be provided to regulatory authorities if required. I understand that I may have certain rights under applicable data privacy laws regarding my personal information, including the right to access my personal information held by BioComp. For further information regarding these rights, please reference BioComp's Privacy Policy. I understand that I may opt out of continued receipt of such communications at any time by emailing Compliance@tiopronin.com. Receipt of these communications is not required to receive BioComp patient support services.

TEXT MESSAGING CONSENT

I acknowledge that by checking the text message consent box below, I expressly consent to receive text messages or automated calls from or on behalf of BioComp at the mobile phone number(s) that I provide.

I confirm that I am the subscriber for the mobile phone number(s) provided, and I agree to notify BioComp promptly if any of my number(s) change in the future. I understand that my wireless service provider's message and data rates may apply to any text messages that I receive from or on behalf of BioComp at the mobile phone number(s) that I provide. I understand that I can opt out of future text messages at any time by written notice to BioComp.

I understand that my consent to receiving text messages from or on behalf of BioComp is not required as a condition of purchasing any goods or services from BioComp or its affiliates.

OPTIONAL – ☐ Check this box to agree to receive text messages.

REQUIRED – By signing below, I certify that I have read and understand the BioComp MyCare Solutions Program Authorization and agree to its terms.

SIGN & DATE

Printed name if signed by legal representative.

Relationship to patient

Please see full Prescribing Information on pages 5-8

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Tiopronin Delayed-Release Tablets safely and effectively.

See full prescribing information for Tiopronin Delayed-Release Tablets.

Tiopronin Delayed-Release Tablets
delayed-release tablets, for oral use
Initial U.S. Approval: 1988

----------INDICATIONS AND USAGE----------

Tiopronin Delayed-Release Tablets are a reducing and complexing thiol indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are not responsive to these measures alone. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dosage was about 1,000 mg/day. (2.1)
- The recommended initial dosage in pediatric patients 20 kg and greater is 15 mg/kg/day. Avoid dosages greater than 50 mg/kg per day in pediatric patients. (5.1, 8.4)
- Measure urinary cystine 1 month after initiation of Tiopronin Delayed-Release Tablets and every 3 months thereafter (2.3)
- Administer Tiopronin Delayed-Release Tablets in 3 divided doses at the same times each day, with or without food. Maintain a routine pattern with regard to meals. (2.1)
- Tiopronin Delayed-Release Tablets can be crushed and mixed with applesauce. For preparation and administration instructions, see the full prescribing information. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 100 mg and 300 mg (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to tiopronin or any component of Tiopronin Delayed-Release Tablets (4)

----------WARNINGS AND PRECAUTIONS----------

- Proteinuria, including nephrotic syndrome, and membranous nephropathy, has been reported with tiopronin use. Pediatric patients receiving greater than 50 mg/kg of tiopronin per day may be at increased risk for proteinuria. (2.1, 5.1, 8.4)
- Hypersensitivity reactions have been reported during tiopronin treatment. (4, 5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥10%) are nausea, diarrhea or soft stools, oral ulcers, rash, fatigue, fever, arthralgia, proteinuria, and emesis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact BioComp Pharma, Inc. at toll-free phone # 1-866-762-2365 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding is not recommended. (8.2)
- Geriatric: Choose dose carefully and monitor renal function in the elderly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tiopronin Delayed-Release Tablets are indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are not responsive to these measures alone.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Adults: The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dosage was about 1,000 mg/day.

Pediatrics: The recommended initial dosage in pediatric patients weighing 20 kg and greater is 15 mg/kg/day. Avoid dosages greater than 50 mg/kg per day in pediatric patients *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.

Administer Tiopronin Delayed-Release Tablets in 3 divided doses at the same times each day, with or without food. Maintain a routine pattern with regard to meals.

Consider starting Tiopronin Delayed-Release Tablets at a lower dosage in patients with history of severe toxicity to d-penicillamine.

2.2 Preparation and Administration Instructions

For patients who cannot swallow the tablet whole, Tiopronin Delayed-Release Tablets can be crushed and mixed with applesauce. Administration of Tiopronin Delayed-Release Tablets with other liquids or foods has not been studied and is not recommended.

Preparation and Administration of Tiopronin Delayed-Release Tablets Mixed in Applesauce

For patients who can swallow semi-solid food, Tiopronin Delayed-Release Tablets can be crushed and mixed with applesauce:

1. Crush the Tiopronin Delayed-Release Tablet in a clean pill crusher or mortar and pestle. Always crush one tablet at a time.
2. Measure approximately one tablespoon of applesauce and transfer it into a container with the crushed Tiopronin Delayed-Release Tablet.
3. Mix the crushed Tiopronin Delayed-Release Tablet in the applesauce until the powder is well dispersed.
4. Administer the entire Tiopronin Delayed-Release Tablets-applesauce mixture to the patient's mouth immediately. (However, if this is not possible, the mixture can be stored in a refrigerator for up to 2 hours after adding the crushed tablet to the applesauce. Discard any mixture that has not been given within 2 hours.)
5. To assure that any leftover applesauce mixture from the container is recovered, add tap water to the same container, mix, and have the patient drink the water.

2.3 Monitoring

Measure urinary cystine 1 month after starting Tiopronin Delayed-Release Tablets and every 3 months thereafter. Adjust Tiopronin Delayed-Release Tablets dosage to maintain urinary cystine concentration less than 250 mg/L.

Assess for proteinuria before treatment and every 3 to 6 months during treatment *[see Warnings and Precautions (5.1)]*.

Discontinue Tiopronin Delayed-Release Tablets in patients who develop proteinuria, and monitor urinary protein and renal function. Consider restarting Tiopronin Delayed-Release Tablets treatment at a lower dosage after resolution of proteinuria.

3 DOSAGE FORMS AND STRENGTHS

Tablets for oral use:
100 mg tablets: round, white to off-white and imprinted in red with "T1" on one side
300 mg tablets: round, white to off-white and imprinted in red with "T3" on one side

4 CONTRAINDICATIONS

Tiopronin Delayed-Release Tablets are contraindicated in patients with hypersensitivity to tiopronin or any other components of Tiopronin Delayed-Release Tablets *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Proteinuria

Proteinuria, including nephrotic syndrome, and membranous nephropathy, have been reported with tiopronin use. Pediatric patients receiving greater than 50 mg/kg of tiopronin per day may be at increased risk for proteinuria *[see Dosage and Administration (2.3), Adverse Reactions (6.1, 6.2), Use in Specific Populations (8.4)]*. Monitor patients for the development of proteinuria and discontinue therapy in patients who develop proteinuria *[see Dosage and Administration (2.3)]*.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions (drug fever, rash, fever, arthralgia and lymphadenopathy) have been reported *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Proteinuria *[see Warnings and Precautions (5.1)]*
- Hypersensitivity *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of the drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions occurring at an incidence of ≥5% in an uncontrolled trial in 66 patients with cystinuria age 9 to 68 years are shown in the table below. Patients in group 1 had previously been treated with d-penicillamine; those in group 2 had not. Of those patients who had stopped taking d-penicillamine due to toxicity (34 out of 49 patients in group 1), 22 were able to continue treatment with Tiopronin Tablets. In those without prior history of d-penicillamine treatment, 6% developed reactions of sufficient severity to require Tiopronin Tablets withdrawal.

Table 1 presents adverse reactions ≥5% in either treatment group occurring in this trial.

Table 1: Adverse Reactions Occurring in One or More Patients

System Organ Class	Adverse Reaction	Group 1 Previously treated with d-penicillamine (N = 49)	Group 2 Naïve to d-penicillamine (N = 17)
Blood and Lymphatic System Disorders	anemia	1 (2%)	1 (6%)
Gastrointestinal Disorders	nausea	12 (25%)	2 (12%)
	emesis	5 (10%)	–
	diarrhea/soft stools	9 (18%)	1 (6%)
	abdominal pain	–	1 (6%)
	oral ulcers	6 (12%)	3 (18%)
General Disorders and Administration Site Conditions	fever	4 (8%)	–
	weakness	2 (4%)	2 (12%)
	fatigue	7 (14%)	–
	peripheral (edema)	3 (6%)	1 (6%)
	chest pain	–	1 (6%)
Metabolism and Nutrition Disorders	anorexia	4 (8%)	–
Musculoskeletal and Connective Tissue Disorders	arthralgia	–	2 (12%)
Renal and Urinary Disorders	proteinuria	5 (10%)	1 (6%)
	impotence	–	1 (6%)
Respiratory, Thoracic and Mediastinal Disorders	cough	–	1 (6%)
Skin and Subcutaneous Tissue Disorders	rash	7 (14%)	2 (12%)
	ecchymosis	3 (6%)	–
	pruritus	2 (4%)	1 (6%)
	urticaria	4 (8%)	–
	skin wrinkling	3 (6%)	1 (6%)

Taste Disturbance

A reduction in taste perception may develop. It is believed to be the result of chelation of trace metals by tiopronin. Hypogeusia is often self-limited.

6.2 Postmarketing Experience

Adverse reactions have been reported from the literature, as well as during post-approval use of Tiopronin Tablets. Because the post-approval reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tiopronin Tablets exposure.

Adverse reactions reported during the postmarketing use of Tiopronin Tablets are listed by body system in **Table 2.**

Please see full Prescribing Information on pages 5-8

Table 2: Adverse Reactions Reported for Tiopronin Tablets Pharmacovigilance by System Organ Class and Preferred Term

System Organ Class	Preferred Term
Cardiac Disorders	congestive heart failure
Ear and Labyrinth Disorder	vertigo
Gastrointestinal Disorders	abdominal discomfort; abdominal distension; abdominal pain; chapped lips; diarrhea; dry mouth; dyspepsia; eructation; flatulence; gastrointestinal disorder; gastroesophageal reflux disease; nausea; vomiting; jaundice; liver transaminitis
General Disorders and Administration Site Conditions	asthenia; chest pain; fatigue; malaise; pain; peripheral swelling; pyrexia; swelling
Investigations	glomerular filtration rate decreased; weight increased
Metabolism and Nutrition Disorders	decreased appetite; dehydration; hypophagia
Musculoskeletal and Connective Tissue Disorders	arthralgia; back pain; flank pain; joint swelling; limb discomfort; musculoskeletal discomfort; myalgia; neck pain; pain in extremity
Nervous System Disorders	ageusia; burning sensation; dizziness; dysgeusia; headache; hypoesthesia
Renal and Urinary Disorders	nephrotic syndrome; proteinuria; renal failure
Skin and Subcutaneous Tissue Disorders	dry skin; hyperhidrosis; pemphigus foliaceus; pruritus; rash; rash pruritic; skin irritation; skin texture abnormal; skin wrinkling; urticaria

7 DRUG INTERACTIONS

7.1 Alcohol

Tiopronin is released faster from Tiopronin Delayed-Release Tablets in the presence of alcohol and the risk for adverse events associated with Tiopronin Delayed-Release Tablets when taken with alcohol is unknown. Avoid alcohol consumption 2 hours before and 3 hours after taking Tiopronin Delayed-Release Tablets *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available published case report data with tiopronin have not identified a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Renal stones in pregnancy may result in adverse pregnancy outcomes *(see Clinical Considerations)*. In animal reproduction studies, there were no adverse developmental outcomes with oral administration of tiopronin to pregnant mice and rats during organogenesis at doses up to 2 times a 2 grams/day human dose (based on mg/m^2). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Renal stones in pregnancy may increase the risk of adverse pregnancy outcomes, such as preterm birth and low birth weight.

Data

Animal Data

No findings of fetal malformations could be attributed to the drug in reproduction studies in mice and rats at doses up to 2 times the highest recommended human dose of 2 grams/day (based on mg/m^2).

8.2 Lactation

Risk Summary

There are no data on the presence of tiopronin in either human or animal milk or on the effects of the breastfed child. A published study suggests that tiopronin may suppress milk production. Because of the potential for serious adverse reactions, including nephrotic syndrome, advise patients that breastfeeding is not recommended during treatment with Tiopronin Delayed-Release Tablets.

8.4 Pediatric Use

Tiopronin Delayed-Release Tablets are indicated in pediatric patients weighing 20 kg or more with severe homozygous cystinuria, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation who are not responsive to these measures alone. This indication is based on safety and efficacy data from a trial in patients 9 years to 68 years of age and clinical experience. Proteinuria, including nephrotic syndrome, has been reported in pediatric patients. Pediatric patients receiving greater than 50 mg/kg tiopronin per day may be at greater risk *[see Dosage and Administration (2.1, 2.3), Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Tiopronin Delayed-Release Tablets are not approved for use in pediatric patients weighing less than 20 kg *[see Dosage and Administration (2.1)]*.

8.5 Geriatric Use

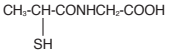
This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

There is no information on overdosage with tiopronin.

11 DESCRIPTION

Tiopronin Delayed-Release Tablets are a reducing and cystine-binding thiol drug (CBTD) for oral use. Tiopronin is N-(2-Mercaptopropionyl) glycine and has the following structure:



Tiopronin has the empirical formula $C_5H_9NO_3S$ and a molecular weight of 163.20. In this drug product tiopronin exists as a dl racemic mixture.

Tiopronin is a white crystalline powder, which is freely soluble in water.

Each Tiopronin Delayed-Release Tablet contains 100 or 300 mg of tiopronin. The inactive ingredients in Tiopronin Delayed-Release Tablets include lactose monohydrate, hydroxypropyl cellulose, hydroxypropyl cellulose (low substitute), magnesium stearate, hydroxypropyl methylcellulose E5, methacrylic acid: ethyl acrylate copolymer (Eudragit L 100-55), talc, triethyl citrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The goal of therapy is to reduce urinary cystine concentration below its solubility limit. Tiopronin is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form a mixed disulfide of tiopronin-cysteine. From this reaction, a water-soluble mixed disulfide is formed and the amount of sparingly soluble cystine is reduced.

12.2 Pharmacodynamics

The decrement in urinary cystine produced by tiopronin is generally proportional to the dose. A reduction in urinary cystine of 250-350 mg/day at tiopronin dosage of 1 g/day, and a decline of approximately 500 mg/day at a dosage of 2 g/day, might be expected. Tiopronin has a rapid onset and offset of action, showing a fall in cystine excretion on the first day of administration and a rise on the first day of drug withdrawal.

12.3 Pharmacokinetics

Absorption

Tiopronin Delayed-Release Tablets

When Tiopronin Tablets and Tiopronin Delayed-Release Tablets single doses were given to fasted healthy subjects, the median time to peak plasma levels (T_{max}) was 1 (range: 0.5 to 2.1) and 3 (range: 1.0 to 6.0) hours, respectively. The peak exposure (C_{max}) and total exposure (AUC_{0-t}) of tiopronin from Tiopronin Delayed-Release Tablets were decreased by 22% and 7% respectively compared to Tiopronin Tablets.

When Tiopronin Delayed-Release Tablets were administered crushed in applesauce, the median time to peak plasma levels of tiopronin (T_{max}) was 1 hour (range: 0.5 to 2.0) compared to 3.1 hours (range: 1.5 to 4.0) when administered as intact Tiopronin Delayed-Release Tablets.

When Tiopronin Delayed-Release Tablets were administered crushed in applesauce, the maximum concentration (C_{max}) and exposure (AUC_{0-t}) to tiopronin were increased by 38% and 14%, respectively, compared to Tiopronin Delayed-Release Tablets administered intact.

Food Effects

Administration of the Tiopronin Delayed-Release Tablet with food decreases C_{max} of tiopronin by 13% and AUC_{0-t} by 25% compared to Tiopronin Delayed-Release Tablets administered in a fasted state.

Since the drug is dosed to effect, the study results support administration of Tiopronin Delayed-Release Tablets with or without food; administer at the same time each day with a routine pattern with regard to meals.

Elimination

Excretion

When tiopronin is given orally, up to 48% of dose appears in urine during the first 4 hours and up to 78% by 72 hours.

Drug Interactions

Alcohol

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40%) on the dose dumping of Tiopronin Delayed-Release Tablets. The study results showed that the addition of alcohol to the dissolution media increases the dissolution rate of Tiopronin Delayed-Release Tablets in the acidic media of 0.1N HCl *[see Drug Interactions (7.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in animals have not been performed.

Mutagenesis

Tiopronin was not genotoxic in the chromosomal aberration, sister chromatid exchange, and *in vivo* micronucleus assays.

Impairment of Fertility

High doses of tiopronin in experimental animals have been shown to interfere with maintenance of pregnancy and viability of the fetus. In 2 published male fertility studies in rats, tiopronin at 20 mg/kg/day intramuscular (IM) for 60 days induced reductions in testis, epididymis, vas deferens, and accessory sex glands weights and in the count and motility of cauda epididymal sperm.

16 HOW SUPPLIED/STORAGE AND HANDLING

100 mg delayed-release, round, white to off-white tablet imprinted with "T1" on one side with red ink and blank on the other side: Bottles of 300 **NDC** 44523-054-01.

300 mg delayed-release, round, white to off-white tablet imprinted with "T3" on one side with red ink and blank on the other side: Bottles of 90 **NDC** 44523-055-01.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Administration Instructions

For patients who cannot swallow the tablet whole, the Tiopronin Delayed-Release Tablets can be crushed and mixed with applesauce. *See Dosage and Administration (2.2)* for preparation and administration instructions.

Lactation

Advise women that breastfeeding is not recommended during treatment with Tiopronin Delayed-Release Tablets *[see Use in Specific Populations (8.2)]*.

BioComp Pharma.

L05501R0721

Manufactured for: BioComp Pharma, Inc.
by Mission Pharmacal Company
San Antonio, TX 78230 1355

BCP_T12767R0323

Please see full Prescribing Information on pages 5-8

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use POTASSIUM CITRATE safely and effectively. See full prescribing information for POTASSIUM CITRATE.

POTASSIUM CITRATE Extended-release tablets for oral use

Initial U.S. Approval: 1985

----------INDICATIONS AND USAGE----------

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

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

----------DOSAGE 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 mEq per day; a dose of 30 mEq two times per day or 20 mEq three times per day with meals or within 30 minutes after meals or bedtime snack (2.2)
- Mild to moderate hypocitraturia (urinary citrate >150 mg/day): therapy should be initiated at 30 mEq per day; a dose of 15 mEq two times per day or 10 mEq three times per day with meals or within 30 minutes after meals or bedtime snack (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mEq and 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/kg/min) (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 myocardial 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 BioComp Pharma, Inc. 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 anticholinergics) can be expected to increase the gastrointestinal irritation produced by potassium salts (7.2)
- Renin-angiotensin-aldosterone inhibitors: Monitor for hyperkalemia (7.3)
- Nonsteroidal Anti-inflammatory drugs (NSAIDs) monitor for hyperkalemia (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnant women: 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 capacity. 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)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Renal Tubular Acidosis (RTA) with Calcium Stones

Potassium citrate is indicated for the management of renal tubular acidosis *[see Clinical Studies (14.1)]*.

1.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

Potassium citrate is indicated for the management of Hypocitraturic calcium oxalate nephrolithiasis *[see Clinical Studies (14.2)]*.

1.3 Uric Acid Lithiasis with or without Calcium Stones

Potassium citrate is indicated for the management of Uric acid lithiasis with or without calcium stones *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Instructions

Treatment with extended release potassium citrate 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 Potassium Citrate is to provide Potassium Citrate 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 or 7.0.

Monitor serum electrolytes (sodium, potassium, chloride and carbon dioxide), serum creatinine and complete blood counts every four months and more frequently in patients with cardiac disease, renal disease or acidosis. Perform electrocardiograms periodically. Treatment should be discontinued if there is hyperkalemia, a significant rise in serum creatinine or a significant fall in blood hematocrit or hemoglobin.

2.2 Severe Hypocitraturia

In patients with severe hypocitraturia (urinary citrate < 150 mg/day), therapy should be initiated at a dosage of 60 mEq/day (30 mEq two times/day or 20 mEq three times/day with meals or within 30 minutes after meals or bedtime snack). 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 Potassium Citrate greater than 100 mEq/day have not been studied and should be avoided.

2.3 Mild to Moderate Hypocitraturia

In patients with mild to moderate hypocitraturia (urinary citrate > 150 mg/day) therapy should be initiated at 30 mEq/day (15 mEq two times/day or 10 mEq three times/day with meals or within 30 minutes after meals or bedtime snack). 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. Doses of Potassium Citrate greater than 100 mEq/day have not been studied and should be avoided.

3 DOSAGE FORMS AND STRENGTHS

- 10 mEq tablets are uncoated, tan to yellowish in color, elliptical shaped, with M10 debossed on one side and blank on the other
- 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 urea-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 might promote further bacterial growth.
- 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.

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 myocardial damage or heart failure, should be avoided. Closely monitor for signs of hyperkalemia with periodic blood tests and ECGs.

5.2 Gastrointestinal Lesions

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 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 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 during Potassium Citrate 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 snacks, or by reducing the dosage. Patients may find intact matrices in their feces.

7 DRUG INTERACTIONS

7.1 Potential Effects of Potassium Citrate on Other Drugs

Potassium-sparing Diuretics: 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

Drugs that slow gastrointestinal transit time: These agents (such as anticholinergics) can be expected to increase the gastrointestinal irritation produced by potassium salts.

7.3 Renin-Angiotensin-Aldosterone System Inhibitors

Drugs that inhibit the renin-angiotensin-aldosterone system

Please see full Prescribing Information on pages 5-8

(RAAS) including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), spironolactone, eplerenone, or aliskiren 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 Potassium Citrate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Potassium Citrate 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 Potassium Citrate has an effect on this content. Potassium Citrate 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

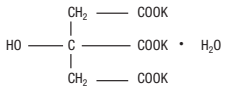
Treatment of Overdosage: The administration of potassium salts to persons without predisposing conditions for hyperkalemia rarely causes serious hyperkalemia at recommended dosages. It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum 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. 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, potato (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 300-500 mL/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 mL. 6. Correction of acidosis, if present, with intravenous sodium bicarbonate. 7. Hemodialysis or peritoneal dialysis. 8. Exchange resins may be used. However, this measure alone is not sufficient for the acute treatment of hyperkalemia.

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

11 DESCRIPTION

Potassium Citrate is a citrate salt of potassium. Its empirical formula is $K_3C_6H_5O_7 \cdot H_2O$, and it has the following chemical structure:



Potassium Citrate yellowish to tan, oral wax-matrix tablets, contain 10 mEq (1080 mg) potassium citrate and 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 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, Potassium Citrate 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 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 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 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.

14 CLINICAL STUDIES

The pivotal Potassium Citrate 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 overstate 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 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 restricted diet (100 mEq/day) and to reduce oxalate intake (limited intake of nuts, dark roughage, chocolate and tea). A moderate calcium restriction (400-800 mg/day) was imposed on patients with hypercalciuria.

X-rays of the urinary tract, available in all patients, were reviewed carefully 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 on-treatment phase. While it is likely that these patients passed pre-existing stones during therapy, the most conservative assumption is that the passed stones were newly formed. Using this assumption, the stone-passage remission 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±27 to 1±2 per year.

14.2 Hypocitraturic Calcium Oxalate Nephrolithiasis of any Etiology

Eighty-nine patients with hypocitraturic calcium nephrolithiasis or uric acid lithiasis with or without calcium nephrolithiasis participated in this 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 diarrheal 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 hypocitraturia. 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 oxalate nephrolithiasis, 4 with uric acid lithiasis accompanied by calcium stones and 2 with hypocitraturia and hyperuricemia accompanied by calcium stones. The dose of potassium citrate ranged from 30 to 100 mEq 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 from 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 hyperuricemia. 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 In Patients With Calcium Oxalate Nephrolithiasis.

	Stones Formed Per Year			
Group	Baseline	On Treatment	Remission*	Any Decrease
I (n=19)	12 ± 30	0.9 ± 1.3	58%	95%
II (n=37)	1.2 ± 2	0.4 ± 1.5	89%	97%
III (n=15)	4.2 ± 7	0.7 ± 2	67%	100%
IV (n=18)	3.4 ± 8	0.5 ± 2	94%	100%
Total (n=89)	4.3 ± 15	0.6 ± 2	80%	98%

*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 uric acid and calcium salts or formed both uric acid 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 hyperuricemia with gouty arthritis, symptomatic hyperuricemia, or hyperuricosuria. One patient also received hydrochlorothiazide because of unclassified hypercalciuria. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Potassium Citrate 10 mEq tablets are uncoated, tan to yellowish in color, elliptical shaped, with M10 debossed on one side and blank on the other, supplied in bottles as:

NDC 44523-410-01 Bottle of 100

Potassium Citrate 15 mEq tablets are uncoated, tan to yellowish in color, modified rectangle shaped, with M15 debossed on one side and blank on the other, supplied in bottles as:

NDC 44523-415-01 Bottle of 100

Storage: Store in a tight container.

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 both diuretics and digitalis 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 check with the doctor 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.

BioComp Pharma.

L41001R1224

Manufactured for:
BioComp Pharma, Inc.
San Antonio, TX 78230 1355

BCP_T13899R0125

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