

Contains Nonbinding Recommendations

Draft Guidance on Potassium Citrate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Potassium Citrate

Form/Route: Extended Release Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 15 mEq x 4 tablets (60 mEq dose)
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see additional comments below.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 15 mEq x 4 tablets (60 mEq dose)
Subjects: Healthy males and nonpregnant females, general population
Additional Comments: Please see additional comments below.

Additional comments applicable to both bioequivalence studies:

- 1) Please note that the standardized diet used for potassium chloride studies may not be the appropriate diet for potassium citrate studies. Please review the available literature on potassium citrate bioavailability to develop a standardized diet for citrate for the study.
- 2) For the potassium analyte, you may refer to the draft guidance "Potassium Chloride Modified Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing" for designing and conducting the bioequivalence study. A protocol addressing your proposal for the citrate component may be submitted for review.
- 3) It is recommended that baseline excretion of potassium and citrate (obtained during the baseline studies) be subtracted from the amount obtained on the drug dosing day to yield the net effect of drug administration. The baseline data used should be the average of the two readings obtained on the two baseline days and be subject specific and period specific. Of the baseline-corrected rate of excretion or amount excreted at a particular time interval is negative, the recommendation is to set the value to zero.

- 4) The following information on urine potassium and citrate concentration data is to be recorded for each subject:

Amount excreted in each collection interval (Ae)
Cumulative urinary excretion from 0-24 hours (AeO-24h)
Cumulative urinary excretion from 0-48 hours (AeO-48h)
Maximal rate of urinary excretion (Rmax)
Time of Maximal urinary excretion (Tmax)
Excretion rate in each collection interval (R)
Midpoint of each collection interval (t)

It is recommended that all data are calculated using baseline adjusted and non-baseline adjusted data. Statistical analysis ($p=0.05$) would then be done by ANOVA for baseline adjusted parameters, and the 90 percent confidence intervals generated for natural log-transformed cumulative urinary excretion from 0-24 (AeO-24hr) and maximal rate of urinary excretion data (Rmax). The two one-sided tests procedure can be used to determine 90 percent confidence intervals.

Analytes to measure (in appropriate biological fluid): Potassium and citrate in urine. For each study, individual and mean urine pH values should be submitted for all collection intervals (including the pre-dose interval) for the test and reference products.

Bioequivalence based on (90% CI): Potassium and citrate in urine

Waiver request of in-vivo testing: 5 mEq and 10 mEq based on (i) acceptable bioequivalence study on the 15 mEq strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.