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# Guidance for Industry

*The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.*

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Potassium Chloride
CR Tablet/Capsule
No ANDA #

Revised
JUN - 6 1994

# REVIEW OF A COMMUNICATION

The firm is seeking information about the design of the bioequivalence study for CR Potassium Chloride Tablet or Capsule. It wants to know which is the proper guidance for this drug product. The firm has asked following questions :

1. Is the Guidance published on May 15, 1987 for CR Potassium Chloride Tablet still valid ?

2. Is the general guidance for the controlled-release solid oral dosage forms, published in September 1993, applicable for this drug product ?

3. If former guidance is valid then does the design need KCl solution administration along with administration of CR oral, solid dosage form (test and reference) ?

The answer to the questions are written down as the comments.

# COMMENTS :

1. The 1987 guidance for CR Potassium Chloride is still valid with some modification. The modifications are mentioned in the comment 4.

2. The 1993 guidance for CR solid dosage form is not applicable for this drug product (CR Potassium Chloride oral, solid dosage form).

3. The KCl solution arm mentioned in 1987 guidance for CR Potassium Chloride guidance is no longer necessary. A two-treatment, two period (crossover and head to head), single dose, fasting study is necessary for this drug product.

4. Following precautions are necessary for the study :

   i) Subjects are to be housed in a climate controlled environment so they don't lose potassium through sweat.

ii) The subjects ought to be hydrated at regular time intervals throughout (during equilibrium phase and drug administration) the study so that sufficient amount of urine is obtained.

iii) The subjects should receive definite amount of potassium, sodium, water and calories in daily diet throughout the study.

iv) The subject should be equilibrated on the diet for at least four days. On Days five and six the diet equilibration should continue but urine should be collected at the regular time intervals (on each day) to obtain baseline urinary $K^+$ excretion.

v) The subjects should be administered 80 mEq dose and not 40 mEq dose on day seven. The urine collection at regular time intervals should carried out on days 7 and 8. The second administration of same treatment on day 9 and urine collection on days 9 and 10 is unnecessary and the urinary $K^+$ excretion data for the second administration will not be acceptable for statistical evaluation.

vi) The diet should continue for days 9, 10, 11 and 12 which allows post treatment 1 equilibration. The equilibration should extend to days 13 and 14 during which urine is collected at regular time interval to obtain the baseline for the second period. The crossed over treatment should be administered on day 15 and the urine should be collected on days 15 and 16.

5. This is probably only CR drug product which does not require multidose (steady state) and food challenge studies.

The firm should be informed of these comments.

MAY 15 1987

Division of Bioequivalence
Guidance for In-Vivo Bioequivalence Study
for Slow-Release Potassium Chloride
Tablets/Capsules

A. Introduction:

Potassium ($K^+$) is the major cation of intracellular fluid and thus is widely distributed in all body tissues and fluids. $K^+$ is essential for maintenance of acid-base balance, isotonicity and electrodynamic characteristics of the cell. Other physiologic functions of $K^+$ include the transmission of nerve impulses; contraction of cardiac, skeletal and smooth muscle tissue; and maintenance of normal renal function.

$K^+$ depletion, or hypokalemia, can occur during prolonged diuretic therapy, hyperaldosteronism, diabetic ketoacidosis or gastrointestinal loss through vomiting or diarrhea. Potassium chloride (KCl) is considered the salt of choice in the treatment of hypokalemia because of the frequency with which hypochloremia accompanies $K^+$ depletion. Liquid KCl, though an effective supplement, hinders patient compliance due to its unpalatable salty taste, inconvenience and tendency to induce gastric disturbances such as nausea, vomiting, diarrhea and abdominal discomfort (more often when given as a liquid).

It is important to note that bioavailability/bioequivalence estimates derived from serum $K^+$ levels tend to be inaccurate because of the homeostatic mechanisms that maintain serum $K^+$ levels within a relatively narrow range. Thus, urinary $K^+$ studies are much more commonly used.

B. Bioequivalence Study Protocol:

1. The study should be conducted with at least 24 healthy normal male subjects required to complete. Subjects eligible for participation should be between the ages of 20 to 40 years, within $\pm$ 10% of ideal body weight and have no obvious signs of serious renal, gastrointestinal (guiac negative), cardiovascular, hepatic, neurological or adrenal-pituitary (e.g., diabetes insipidus or hyperaldosteronism, etc.) disorders as evidenced by medical history, physical exam and clinical laboratory tests. Subjects should be free of all medications for two weeks prior to drug administration until after study completion. Similarly, alcoholic beverages should be avoided for a period of 48 hours prior to drug administration until after study completion.

The subjects should be placed on a standardized diet, with known amounts of $K^+$, Sodium ($Na^+$), calories and fluid. The subjects should receive a low $K^+$ diet (normal daily intake 50-150 mEq/day) of 50-60 mEq/day, a low $Na^+$ diet of 160-180 mEq/day and caloric intake of 2,500-3,500 calories/day. Fluid intake (normally 1300-2500 ml/day) should be on the higher side (3,000-5,000 ml/day) to insure an adequate rate of urine flow throughout the study period. The subjects should be placed in a climate controlled environment (and thus remain in-house as much as possible), with physical activity restricted to avoid excessive sweating (and thus $K^+$ loss). The above ranges quoted for $K^+$, $Na^+$, calories and fluid are meant only to provide an investigator with flexibility when planning a protocol. Otherwise, when an actual study is being run, strict control and knowledge of actual exact amounts is critical for study success. Detailed information regarding the composition of the diet should be included in the final report. Meals, snacks and fluids (see below) should be given at standard times, and subjects should be strongly encouraged to ingest the required amounts (and only those) and refrain from unnecessary physical activity. Additionally, subjects should be queried regarding any prolonged episodes of diarrhea or excessive sweating, as these occurrences may invalidate or obscure the results. Stool guiac tests should be performed on each dosing day.

2. The bioequivalence study should be a single-dose, three-way crossover, with an approved KCl liquid product (20 mEq/15 ml) used as the immediate-release reference. The test 6.7, 8 or 10 mEq tablet or capsule should be compared to a reference 6.7, 8 or 10 mEq tablet or capsule, so long as the comparison is identical regarding dosage form and mEq of K+ per dosage form (that is, a head to head comparison). The reference product can be any 6.7, 8 or 10 mEq tablet or capsule as approved under a full New Drug Application (see the Approved Drug Products with Therapeutic Equivalence Evaluations [Orange] Book). The test product should be from a production lot or from a lot produced under production conditions. Each drug product should be clearly identified by its lot number, and, if applicable, its expiration date. The dose of KCl to be administered should be [redacted] 80 mEq.

3. The following dosing, dietary and urine collection schedule should be used:

Period 1:

Days 1-3: Diet Equilibration Days: standard amounts of Na+, K+, calories and fluids are administered (as outlined above). Fluids should be administered in a schedule similar to: 500 ml initially (at 7 AM), then 200 ml every hour after that for 12 hours. Following that 12 hr point, additional (known) amounts of fluids should be administered at the investigators' discretion. No urine collected.

Days 4-5: Baseline Days: urine is collected each day to establish each subject's baseline level of potassium excretion. The standard diet and fluid schedule continue. Urine is collected in the following manner:

Day 4: subjects void urine sample at 7 AM, then urine is collected at 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16 and 16-24 hours.
Day 5: as for Day 4, without voiding 7AM sample.

Day 6: Drug Dosing Day: standard diet and fluids continue. [redacted]80 mEq of either KCl liquid or test capsule/tablet or reference capsule/tablet are given at 7 AM with 500 ml. Subjects should be instructed to remain upright for 3 hours following dosing. Urine should be collected as outlined in Day 5 above: at 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16 and 16-24 hours.

Period 2:

Days 1 and 2 of period 2 (study days 7-8) represent the Diet Equilibration Days/Washout Period, as outlined above in period 1.
Days 3 and 4 of period 2 represent the Baseline Days as outlined for period 1.
Day 5 of period 2 represents the Drug Dosing Day, where treatments are crossed over (each subject receives a preparation different from the one received in period 1).

Period 3:

Days 1 and 2 of period 3 (study days 12 and 13) represent the Diet Equilibration Days/Washout Period as outlined above in phase 1.
Days 3 and 4 of period 3 represent the Baseline Days as outlined for period 1.
Day 5 of period 3 represents the Drug Dosing Day, where treatments are crossed over (each subject receives a preparation different from the ones received in periods 1 and 2).

The study protocol should be approved by an Institutional Review Board. Written informed consent should be obtained from each subject.

4. Assay: The assay for $K^+$ in urine should be validated for sensitivity, specificity (especially in the presence of other commonly occurring cations in urine, such as $Na^+$), stability of $K^+$ in urine, precision, accuracy and linearity. This information should be included in the final bioequivalence study report. The most widely used assay for the determination of K+ in urine is flame photometry.

5. Data Analysis: To assure adequate urine collections during the Baseline and Drug Dosing Days, all urine collected during those days should also be used to determine creatinine clearance.

Baseline excretion of K+ (obtained during the Baseline Days) should be subtracted from that 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 phase specific (e.g. for subject #12, his phase II amount of baseline excretion should only be used to adjust his phase II drug dosing day amount). Although fluctuations in the baseline are expected, differences in baseline excretion amounts for the two Baseline Days certainly should not differ by more than 100%.

Urine data for each subject should be used to calculate the following mean data for each product: Cumulative urinary excretion from 0-24 hours, the maximal rate of urinary excretion (Rmax), the time of maximal urinary excretion (Tmax) and a rate profile (rates at 0-1, 1-2 . . . 16-24 hours). Statistical analysis ($p = 0.05$) should be done by ANOVA and by analysis of co-variance for cumulative 0-24 excretion, Rmax, Tmax and rate profile. If differences are detected amongst the three products, Duncan's Multiple Range test or student's t-test (or any other suitable test) should be performed to detect where these differences occur. Using the error terms obtained by both ANOVA and analysis of covariance, the following statistical parameters should be calculated for cumulative 0-24, Rmax and Tmax:

the power of the study to detect differences of 20% of the reference means (should they exist) at alpha = 0.05; 90% confidence intervals using the two one-sided t-test; and, Westlake's 95% symmetrical confidence intervals.

C. Bioequivalence Requirements for Other Strengths of Capsules/Tablets:

The bioequivalence requirement for another strength of KCl capsule or tablet will be deemed to have been met under either of the following conditions:

1. an approved bioequivalence study for this strength, or
2. evidence of all the following conditions
    a. for a test capsule:
        i. the capsule is proportionally similar with respect to active and inactive ingredient formulation to that capsule that underwent an acceptable in-vivo bioequivalence study
        ii. the capsule has satisfactory dissolution testing performance compared to a reference (identical strength) capsule.
    b. for a tablet, this applies exclusively to those tablets with slow-release beads (encapsulated granules):
        i. the tablet is proportionally similar with respect to active and inactive ingredient formulation to that tablet that underwent an acceptable in-vivo bioequivalence study
        ii. the tablet has satisfactory dissolution testing performance compared to a reference (identical strength) tablet.
3. A tablet with a prolonged-release mechanism other than that stated in 2b above cannot qualify for waiver of a bioequivalence study and must undergo a full in-vivo bioequivalence study.

D. Dissolution Testing:

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| Apparatus: | For Capsules: USP XXI apparatus I (basket) at 100 rpm<br>For Tablets: USP XXI apparatus II (paddle) at 50 rpm |
| Media: | 1. 900 ml of Simulated gastric fluid (without enzymes) for hours 0-1, then 900 ml of a modified simulated intestinal fluid (without enzymes and a phosphate buffer not containing potassium) for hours 1-8, all at 37°C.<br><br>2. 900 ml of deaerated water at 37°C for 8 hours. |
| Reference Drug: | respective comparative strength and dosage form reference product (as approved under a full NDA). |
| Number of Dosage Units Tested: | 12 units of each the reference and test products (the same lots used in the bioequivalence study, if applicable). |
| Sampling Times/Specification: | Appropriate dissolution specifications should be proposed at 1, 3 or 4 and 8 hours. |

Dissolution data should be summarized to show mean and coefficient of variation for each sampling time point for both test and reference products.

E. References:

Pharmacokinetic References:


1. Arnold J., et. al. Bioavailability and Pharmacokinetics of a New, Slow-Release Potassium Chloride Capsule. J. Pharm. Sci. 1980; 69(12): 1416-1418.

2. Ben-Ishay D., et. al. Bioavailability of potassium from a slow-release tablet. Clin. Pharm. Therap. 1973; 14(2): 250-8.

3. Skoutakis, VA, et. al. Liquid and Solid Potassium Chloride: Bioavailability and Safety. Pharmacother. 1984; 4:392-7.

4. Skoutakis VA, et. al. The Comparative Bioavailability of Liquid, Wax-Matrix, and Microencapsulated Preparations of Potassium Chloride. J. Clin. Pharmacol. 1985; 25: 619-21.

Assay References (Photometric):

1. Bauer, J. et. al., "Bray's Clinical Laboratory Methods," C.V. Mosby, St. Louis, Mo., 1962, pp 68,69.

2. Tritz, NW, ed. Fundanentals of Clinical Chemistry, 2nd ed.,Saunders, 1976.

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