CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 77-419

Name: Potassium Chloride Extended Release Capsules, 8 mEq and 10 mEq

Sponsor: Andrx Pharmaceuticals

Approval Date: June 2, 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-419

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-419

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-419

Andrx Pharmaceuticals, LLC
Attention: Janet Vaughn
Director, Regulatory Affairs
2945 W. Corporate Lakes Blvd.
Weston, FL 33331

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 1, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq.

Reference is also made to your amendments dated May 20, and August 16, 2005; February 16, 2006; and April 29, 2008.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved effective on the date of this letter. The Division of Bioequivalence has determined your Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Micro-K ExtenCaps, 8 mEq and 10 mEq, respectively, of KV Pharmaceutical Company. Your dissolution testing should be conducted as specified in the USP, and should be incorporated into the stability and quality control program.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert L. West
6/2/2008 09:27:49 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-419

LABELING

Andrx
PHARMACEUTICALS, INC.

POTASSIUM CHLORIDE

EXTENDED-RELEASE CAPSULES, USP

(600 mg)
8 mEq K

Rx ONLY

100 Capsules

Potassium Chloride Extended-release capsules, USP 8 mEq contain microencapsulated KCl and are designed to release the active ingredient over an 8-to-10-hour period.

Usual Dosage: See accompanying package insert.

Dispense in a tight container as defined in the USP.

Store at controlled room temperature 20°- 25°C (68°-77°F).

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7578 (09/04)

3 62037 55901 3

LOT:

EXP:

Andrx PHARMACEUTICALS, INC.

NDC 62037-550-05

POTASSIUM CHLORIDE

EXTENDED RELEASE CAPSULES, USP

(600 mg)
8 mEq K

Rx ONLY

500 Capsules

Potassium Chloride Extended-release capsules, USP 8 mEq contain microencapsulated KCl and are designed to release the active ingredient over an 8-to-10-hour period.

Usual Dosage: See accompanying package insert.

Dispense in a tight container as defined in the USP.

Store at controlled room temperature 20°- 25°C (68°-77°F).

7581 (09/04)

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT:
EXP:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-560-01

POTASSIUM CHLORIDE

EXTENDED-RELEASE CAPSULES, USP

(750 mg)
10 mEq K

Rx ONLY

100 Capsules

Potassium Chloride Extended-release capsules, USP 10 mEq contain microencapsulated KCl and are designed to release the active ingredient over an 8-to-10-hour period.

Usual Dosage: See accompanying package insert.

Dispense in a tight container as defined in the USP.

Store at controlled room temperature 20° to 25°C (68°-77°F).

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7580 (09/04)

3 62037 56001 9

LOT:

EXP:

Andrx
PHARMACEUTICALS, INC.

NDC 62037-560-05

POTASSIUM CHLORIDE

EXTENDED RELEASE CAPSULES, USP

(750 mg)
10 mEq K

Rx ONLY

500 Capsules

Potassium Chloride Extended-release capsules, USP 10 mEq contain microencapsulated KCl and are designed to release the active ingredient over an 8-to-10-hour period.

Usual Dosage: See accompanying package insert.

Dispense in a tight container as defined in the USP.

Store at controlled room temperature 20° to 25°C (68°-77°F).

7579 (09/04)

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

LOT:
EXP:

POTASSIUM CHLORIDE EXTENDED-RELEASE CAPSULES, USP, 8 mEq and 10 mEq

℞ Only

DESCRIPTION:

Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq are oral dosage forms of microencapsulated potassium chloride containing 600 and 750 mg, respectively, of potassium chloride USP equivalent to 8 and 10 mEq of potassium.

Dispersibility of potassium chloride (KCl) is accomplished by microencapsulation and a dispersing agent. The resultant flow characteristics of the KCl microcapsules and the controlled release of K^+ ions by the microcapsular membrane are intended to avoid the possibility that excessive amounts of KCl can be localized at any point on the mucosa of the gastrointestinal tract.

Each crystal of KCl is microencapsulated by a process with an insoluble polymeric coating which functions as a semi-permeable membrane; it allows for the controlled release of potassium and chloride ions over an eight-to-ten-hour period. Fluids pass through the membrane and gradually dissolve the potassium chloride within the micro-capsules. The resulting potassium chloride solution slowly diffuses outward through the membrane. Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq are electrolyte replenishers. The chemical name of the active ingredient is potassium chloride and the structural formula is KCl. Potassium chloride USP occurs as a white, granular powder or as colorless crystals. It is odorless and has a saline taste. Its solutions are neutral to litmus. It is freely soluble in water and insoluble in alcohol.

The inactive ingredients are, ethylcellulose, FD&C blue #1, FD&C red # 40, gelatin, sodium lauryl sulfate, titanium oxide and triacetin.

CLINICAL PHARMACOLOGY: Potassium ion is the principal intracellular cation of most body tissues. Potassium ions participate in a number of essential physiological processes, including the maintenance of intracellular tonicity, the transmission of nerve impulses, the contraction of cardiac, skeletal, and smooth muscle, and the maintenance of normal renal function.

The intracellular concentration of potassium is approximately 150 to 160 mEq per liter. The normal adult plasma concentration is 3.5 to 5 mEq per liter. An active ion transport system maintains this gradient across the plasma membrane.

Potassium is a normal dietary constituent and under steady-state conditions the amount of potassium absorbed from the gastrointestinal tract is equal to the amount excreted in the urine. The usual dietary intake of potassium is 50 to 100 mEq per day.

Potassium depletion will occur whenever the rate of potassium loss through renal excretion and/or loss from the gastrointestinal tract exceeds the rate of potassium intake. Such depletion usually develops slowly as a consequence of therapy with diuretics, primary or secondary hyperaldosteronisms, diabetic ketoacidosis, or inadequate replacement of potassium in patients on prolonged parenteral nutrition.

Depletion can develop rapidly with severe diarrhea, especially if associated with vomiting. Potassium depletion due to these causes is usually accompanied by a concomitant loss of chloride and is manifested by hypokalemia and metabolic alkalosis. Potassium depletion may produce weakness, fatigue, disturbances of cardiac rhythm (primarily ectopic beats), prominent U-waves in the electrocardiogram, and in advanced cases, flaccid paralysis and/or impaired ability to concentrate urine.

If potassium depletion associated with metabolic alkalosis cannot be managed by correcting the fundamental cause of the deficiency, e.g., where the patient requires long-term diuretic therapy, supplemental potassium in the form of high potassium food or potassium chloride may be able to restore normal potassium levels.

In rare circumstances (e.g., patients with renal tubular acidosis) potassium depletion may be associated with metabolic acidosis and hyperchloremia. In such patients potassium replacement should be accomplished with potassium salts other than the chloride, such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH CONTROLLED-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For the treatment of patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxications, and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.

2. For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop e.g., digitalized patients or patients with significant cardiac arrhythmias, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and certain diarrheal states.

The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern and when low doses of the diuretic are used. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, and if dose adjustment of the diuretic is ineffective or unwarranted, supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene, amiloride) (see **OVERDOSAGE**).

Controlled-release formulations of potassium chloride have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium. Potassium supplementation, when indicated in such patients, should be given as a liquid preparation.

All solid oral dosage forms of potassium chloride are contraindicated in any patient in whom there is structural, pathological (e.g., diabetic gastroparesis) or pharmacologic (use of anticholinergic agents or other agents with anticholinergic properties at sufficient dose to exert anticholinergic effects) cause for arrest or delay in capsule passage through the gastrointestinal tract.

WARNINGS:

Hyperkalemia (see OVERDOSAGE)

In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustments.

Interaction with Potassium-Sparing Diuretics

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone, triamterene, or amiloride), since the simultaneous administration of these agents can produce severe hyperkalemia.

Interaction with Angiotensin Converting Enzyme Inhibitors

Angiotensin converting enzyme (ACE) inhibitors (e.g., captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

Gastrointestinal Lesions

Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40 - 50 per 100,000 patient years) compared to sustained-release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric coated products is not available. Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq are microencapsulated capsules formulated to provide a controlled rate of release of microencapsulated potassium chloride and thus to minimize the possibility of high local concentration of potassium near the gastrointestinal wall.

Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after one week of solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix controlled-release formulation under conditions which did not resemble usual or recommended clinical practice (i.e., 96 mEq per day in divided doses of potassium chloride administered to fasted patients, in the presence of an anticholinergic drug to delay gastric emptying). The upper gastrointestinal lesions observed by endoscopy were asymptomatic and were not accompanied by evidence of bleeding (hemoccult testing). The relevance of these findings to the usual conditions (i.e., non-fasting, no anticholinergic agent, smaller doses) under which controlled-release potassium chloride products are used is uncertain; epidemiologic studies have not identified an elevated risk, compared to microencapsulated products, for upper gastrointestinal lesions in patients receiving wax matrix formulations. Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq should be discontinued immediately and the possibility of ulceration, obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occur.

Metabolic Acidosis

Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS:

General The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Information For Patients

Physicians should consider reminding the patient of the following: To take each dose with meals and with a full glass of water or other suitable liquid. To take each dose without crushing, chewing, or sucking the capsules. To take this medicine following the frequency and amount prescribed by the physician. This is especially important if the patient is also taking diuretics and/or digitalis preparations. To check with the physician if there is trouble swallowing capsules or if the capsules seem to stick in the throat.

To check with the physician at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

Laboratory Tests Regular serum potassium determinations are recommended, especially in patients with renal insufficiency or diabetic nephropathy. When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of in vitro hemolysis of the sample.

Drug Interactions Potassium-sparing diuretics, angiotensin converting enzyme inhibitors (see **WARNINGS**).

Carcinogenesis, mutagenesis, impairment of fertility Carcinogenicity, mutagenicity and fertility studies in animals have not been performed. Potassium is a normal dietary constituent.

Pregnancy: Teratogenic Effects: Category C Animal reproduction studies have not been conducted with Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq. It is unlikely that potassium supplementation that does not lead to hyperkalemia would have an adverse effect on the fetus or would affect reproductive capacity.

Nursing Mothers The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use Safety and effectiveness in pediatric patients have not been established.

Geriatric Use Clinical studies of Potassium Chloride Extended-release Capsules did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic 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.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS, AND OVERDOSAGE**). Gastrointestinal bleeding and ulceration have been reported in patients treated with Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq (see **CONTRAINDICATIONS** and **WARNINGS**). In addition to gastrointestinal bleeding and ulceration, perforation and obstruction have been reported in patients treated with other solid KCl dosage forms, and may occur with Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq. The most common adverse reactions to the oral potassium salts are nausea, vomiting, flatulence, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals, or reducing the amount taken at one time. Skin rash has been reported rarely with potassium preparations.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T- waves, loss of P-waves, depression of ST segment, and prolongation of the QT interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of any agents with potassium-sparing properties; (2) intravenous administration of 300 to 500 mL/hr of 10% dextrose solution containing 10 to 20 units of crystalline insulin per 1,000 mL; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis. In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

DOSAGE AND ADMINISTRATION: The usual dietary intake of potassium by the average adult is 50 to 100 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patients. The dose for the prevention of hypokalemia is typically in the range of 20 mEq per day. Doses of 40 to 100 mEq per day or more are used for the treatment of potassium depletion. Dosage should be divided if more than 20 mEq per day is given such that no more than 20 mEq is given in a single dose. Because of the potential for gastric irritation (see **WARNINGS**), Potassium Chloride Extended-release Capsules, USP, 8 mEq and 10 mEq should be taken with meals and with a full glass of water or other liquid.

Patients who have difficulty swallowing capsules may sprinkle the contents of the capsule onto a spoonful of soft food. The soft food, such as applesauce or pudding, should be swallowed immediately without chewing and followed with a glass of cool water or juice to ensure complete swallowing of the microcapsules. The food used should not be hot and should be soft enough to be swallowed without chewing. Any microcapsule/food mixture should be used immediately and not stored for future use.

HOW SUPPLIED: Potassium Chloride Extended-release Capsules, USP, 8 mEq are white opaque capsules, imprinted with Andrx logo on the cap and 559 on the body, each containing 600mg microencapsulated potassium chloride (equivalent to 8 mEq K) in bottles of 100 (NDC 62037-559-01) and bottles of 500 (NDC 62037-559-05)

Potassium Chloride Extended-release Capsules, USP, 10 mEq are dark blue opaque capsules, imprinted with Andrx logo on the cap and 560 on the body, each containing 750 mg microencapsulated potassium chloride (equivalent to 10 mEq K) in bottles of 100 (62037-560-01) and bottles of 500 (NDC 62037-560-05).

Store at controlled room temperature, between 20° C and 25° C (68° F and 77° F).
Dispense in tight container.

Manufactured by
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, Florida 33314

Rev. date: 09/04

7582

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-419

LABELING REVIEWS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 77-419
Date of Submission: May 20, 2005
Applicant's Name: Andrx Pharmaceuticals, Inc.
Established Name: Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq

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Approval Summary:

1. **Do you have 12 Final Printed Labels and Labeling?** Yes

2. **CONTAINER** – Bottles of 100 (600 mg strength capsule)
   Satisfactory in **final print** as of the May 20, 2005 submission
   \\CDSESUBOGD1\N77419\N_000\2005-05-20\Label 600 mg-100.pdf

3. **CONTAINER** – Bottles of 500 (600 mg strength capsule)
   Satisfactory in **final print** as of the May 20, 2005 submission
   \\CDSESUBOGD1\N77419\N_000\2005-05-20\Label 600 mg-500.pdf

4. **CONTAINER** – Bottles of 100 (750 mg strength capsule)
   Satisfactory in **final print** as of the May 20, 2005 submission
   \\CDSESUBOGD1\N77419\N_000\2005-05-20\Label 750 mg-100.pdf

5. **CONTAINER** – Bottles of 500 (750 mg strength capsule)
   Satisfactory in **final print** as of the May 20, 2005 submission
   \\CDSESUBOGD1\N77419\N_000\2005-05-20\Label 750 mg-500.pdf

6. **PACKAGE INSERT**
   Satisfactory in **final print** as of the May 20, 2005 submission
   \\CDSESUBOGD1\N77419\N_000\2005-05-20\Package Outsert.pdf

7. **Revisions needed post-approval**: None

8. **Patent/ Exclusivities:**
   Patent Data – NDA 18-238

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	*N/A*	N/A	No unexpired patents	N/A	N/A

Exclusivity Data– NDA 18-238

Code	Reference	Expiration	Labeling Impact
N/A	No exclusivities at this time	***N/A***	

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Micro K® ExtenTabs
NDA Number: N 18-238SL-031
NDA Drug Name: Micro K® ExtenTabs
NDA Firm: ; N 18-238/SL-031; Approved August 20, 2003
Date of Approval of NDA Insert and supplement: August 20, 2003; NDA 18-238/S-031
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug, Micro K® ExtenTabs.

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. Labeling was recently approved for NDA 18-238/SL-031 on August 20, 2003 for the RLD, Micro K ® Extentabs.

2. **Storage/Dispensing Conditions:**
   NDA: Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F). Dispense in a tight container as defined in the USP.
   ANDA: Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F). Dispense in a tight container as defined in USP.

   USP: Preserve in tight containers at a temperature not exceeding 30°.
3. **Product Line**:
   The innovator markets their product as follows -
   Both strength capsules in bottles of 100 and 500 tablets (Unit-dose cartons of 100)
   The applicant proposes to market their product as follows –
   Both strengths available in bottles of 100 and 500 capsules.
4. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. (See pg. 6126 and 6130 in volume B. 1.3)
5. **Inactive Ingredients:**
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components appearing in, (Vol B. 1.2 and page 0556)
6. **Container/Closure (See page 0444 and 0445 in Vol B. 1.2)**
   Containers: HDPE
   Closure: CRC closures for the bottles of 100 and non-CRC closures for bottles of 500 tablets.
7. **All manufacturing will be done by** Andrx Pharmaceuticals, Inc. (page 0151 in volume B 1.1)

Date of Review: 5/26/05 Date of Submission: 5/20/05

Primary Reviewer: Jim Barlow Date: 5/26/05

Team Leader: John Grace Date: for John Grace 5/26/05

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cc:

ANDA: 77-419
DUP/DIVISION FILE
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Review

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	77-419
Date of Submission:	December 1, 2004
Applicant's Name:	Andrx Pharmaceuticals, Inc.
Established Name:	Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq

Labeling Deficiencies:

1. **CONTAINER** – Bottles of 100 and 500 tablets
   Satisfactory in **draft** as of the December 1, 2004 submission

2. **PACKAGE INSERT**
   Satisfactory in **draft** as of the December 1, 2004 submission

Please revise your labeling as requested above and submit in final print if you prefer.
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance for industry regarding electronic submissions: Providing Regulatory Submissions in Electronic Format – ANDAs (Issued 6/2002)
(http://www.fda.gov/cder/guidance/5004fnl.htm)
The guidance specifies labeling to be submitted in pdf format. To assist in our review, we request that labeling also be submitted in MS Word format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/cdernew/listserv.html or
http://www.accessdata.fda.gov/scripts/cder/drugsatfda\index.cfm

To facilitate review of your next submission, and in accordance with 21CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

1. The labeling submitted by the firm was based on the most recently approved labeling for this drug product. Labeling was recently approved for NDA 18-238/SL-031 on August 20, 2003 for the RLD, Micro K ® Extentabs.
2. **Patent/ Exclusivities:**

Patent Data – NDA 18-238

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	*N/A*	N/A	No unexpired patents	N/A	N/A

Exclusivity Data– NDA 18-238

Code	Reference	Expiration	Labeling Impact
N/A	No exclusivities at this time	***N/A***	

3. **Storage/Dispensing Conditions:**
   NDA: Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F). Dispense in a tight container as defined in the USP.
   ANDA: Store at controlled room temperature, between 20°C and 25°C (68°F and 77°F). Dispense in a tight container.

   USP: Preserve in tight containers at a temperature not exceeding 30°.
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6. **Inactive Ingredients:**
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components appearing in, (Vol B. 1.2 and page 0556)
7. **Container/Closure (See page 0444 and 0445 in Vol B. 1.2)**
   Containers: HDPE
   Closure: CRC closures for the bottles of 100 and non-CRC closures for bottles of 500 tablets.
8. **All manufacturing will be done by** Andrx Pharmaceuticals, Inc. (page 0151 in volume B 1.1)

Date of Review 2/15/05 Date of Submission: 12/1/04

Primary Reviewer: Jim Barlow Date: 2/15/05

Team Leader: John Grace Date: 3/14/05

cc:

ANDA: 77-419
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\ANDRX\LTRS&REV\77419na1.l.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-419

CHEMISTRY REVIEWS

ANDA 77-419

Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq

Andrx Pharmaceuticals, LLC

Yusuf Amin
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-419

2. REVIEW #: 3

3. REVIEW DATE: 16-MAY-2008

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission Amendment	December 01, 2004 January 11, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	13-MAY-2005
Amendment (Labeling and Bio)	20-MAY-2005
Amendment (Bio)	16-AUG-2005
Amendment (Bio)	16-FEB-2006
Amendment (Final Approval)	29-APR-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Andrx Pharmaceuticals, LLC.
Address:	4955 Orange Drive Fort Lauderdale, Florida 33314
Representative:	Janet Vaughn
Telephone: FAX:	(954) 358-6125 (954) 358-6350

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Potassium Chloride Extended-release Capsules USP

9. LEGAL BASIS FOR SUBMISSION:
   Listed Drug Product: Micro K® approved for KV Pharma approved in NDA 18-238.
   There are no unexpired Patents for this drug product.
   There are no unexpired exclusivities for this product.

10. PHARMACOL. CATEGORY: Used for treatment of Hypokalemia

11. DOSAGE FORM: Extended Release Capsule

12. STRENGTH/POTENCY: 8 mEq and 10 mEq

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
NAME: Potassium Chloride Molecular weight : 74.55
STRUCTURE: KCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]			(b) (4)	3	Adequate	26-MAR-2008	
				4			
				4			
				4			
				4			
				4			
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Micro-K® Extended Release Capsule.	NDA 18-238	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable		
Methods Validation	N/A		
Labeling	Acceptable	26-MAY-2005	J. Barlow
Bioequivalence	Acceptable	16-MAR-2006	P. Nwakama
EA	Acceptable	02-MAR-2005	Y. Amin
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 77-419

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Potassium Chloride is colorless, elongated, prismatic, or cubical Crystals, or White, granular powder.

The drug product is capsules filled with off-white round pellets.

B. Description of How the Drug Product is Intended to be Used

Potassium chloride capsules are used for treatment of Hypokalemia.

The recommended maximum daily dose is 40 to 100 mEq (3.0 to 7.5 g).

C. Basis for Approvability or Not-Approval Recommendation

CMC, Bio, Labeling and EER are acceptable.

7 pages have been withheld as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Yusuf A. Amin
5/30/2008 02:47:46 PM
CHEMIST

Rosario DCosta
6/2/2008 11:53:14 AM
CHEMIST

Dat Doan
6/2/2008 11:58:32 AM
CSO

ANDA 77-419

Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq

Andrx Pharmaceuticals, LLC

Yusuf Amin
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-419

2. REVIEW #: 2

3. REVIEW DATE: 16-JUN-2005

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission Amendment	December 01, 2004 January 11, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment Amendment (Labeling and Bio) Amendment (Bio) Amendment (Bio)	13-MAY-2005 20-MAY-2005 16-AUG-2005 16-FEB-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Andrx Pharmaceuticals, LLC.
Address:	4955 Orange Drive Fort Lauderdale, Florida 33314
Representative:	Janet Vaughn
Telephone: FAX:	(954) 358-6125 (954) 358-6350

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Potassium Chloride Extended-release Capsules USP

9. LEGAL BASIS FOR SUBMISSION:

Listed Drug Product: Micro K® approved for KV Pharma approved in NDA 18-238.
There are no unexpired Patents for this drug product.
There are no unexpired exclusivities for this product.

10. PHARMACOL. CATEGORY: Used for treatment of Hypokalemia

11. DOSAGE FORM: Extended Release Capsule

12. STRENGTH/POTENCY: 8 mEq and 10 mEq

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
NAME: Potassium Chloride Molecular weight : 74.55
STRUCTURE: KCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				1	Adequate	16-JUN-2005	
				4			
				4			
				4			
				4			
				4			
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Micro-K® Extended Release Capsule.	NDA 18-238	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Unsatisfactory		cGMP violations
Methods Validation	N/A		
Labeling	Acceptable	26-MAY-2005	J. Barlow
Bioequivalence	Acceptable	16-MAR-2006	P. Nwakama
EA	Acceptable	02-MAR-2005	Y. Amin
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

Executive Summary

The Chemistry Review for ANDA 77-419

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is not approvable due to multiple cGMP violations

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Potassium Chloride is colorless, elongated, prismatic, or cubical Crystals, or White, granular powder.

The drug product is capsules filled with off-white round pellets.

B. Description of How the Drug Product is Intended to be Used

Potassium chloride capsules are used for treatment of Hypokalemia.

The recommended maximum daily dose is 40 to 100 mEq (3.0 to 7.5 g).

C. Basis for Approvability or Not-Approval Recommendation

CMC is not approvable due to multiple cGMP violations

III. Administrative

A. Reviewer's Signature

Yusuf Amin

B. Endorsements:

HFD-623 Yusuf Amin/Chemist/
HFD-623 A. Mueller/Team Leader
HFD-617 Simon Eng/Project Manager/

C. CC:

ANDA: 77-419

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6 pages have been withheld as b4 (CCI/TS) immediately following this page

cc: ANDA 77-419
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-623 /Y.Amin/ S. Ham for
HFD-623 /A. Mueller, Ph.D./ 7-28-06.
HFD-617 /S. Eng, PM / 7/26/06

F/T by :

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TYPE OF LETTER: Not Approvable, CMC minor due to cGMP violations

ANDA 77-419

Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq

Andrx Pharmaceuticals, LLC

Yusuf Amin
Division of Chemistry I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 77-419

2. REVIEW #: 1

3. REVIEW DATE: March 01, 2005

4. REVIEWER: Yusuf Amin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission Amendment	December 01, 2004 January 11, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Andrx Pharmaceuticals, LLC.
Address:	4955 Orange Drive Fort Lauderdale, Florida 33314
Representative:	Janet Vaughn
Telephone: FAX:	(954) 358-6125 (954) 358-6350

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: N/A
   b) Non-Proprietary Name (USAN): Potassium Chloride Extended-release Capsules USP

9. LEGAL BASIS FOR SUBMISSION:

   Listed Drug Product: Micro K® approved for KV Pharma approved in NDA 18-238.

   There are no unexpired Patents for this drug product.
   There are no unexpired exclusivities for this product.

10. PHARMACOL. CATEGORY: Used for treatment of Hypokalemia

11. DOSAGE FORM: Extended Release Capsule

12. STRENGTH/POTENCY: 8 mEq and 10 mEq

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
NAME: Potassium Chloride Molecular weight : 74.55
STRUCTURE: KCl

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	06-MAY-2003	Reviewed by A.Pendse
				4			
				4			
				4			
				4			
				4			
				4			
				4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA for Micro-K® Extended Release Capsule.	NDA 18-238	Reference Listed Drug

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	24-JAN-2005	J. D'Ambrogio
Methods Validation	N/A		
Labeling	Deficient	3/28/05	J. Barlow
Bioequivalence	Deficient	4/19/05	S. Lu
EA	Acceptable	02-MAR-2005	Y. Amin
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. _X___ Yes ____ No If no, explain reason(s) below:

Executive Summary

The Chemistry Review for ANDA 77-419

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is not approvable at this stage. See text for deficiency comments. There are some minor deficiencies and the firm should address them. Bio and Labeling reviews are also deficient.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Potassium Chloride is colorless, elongated, prismatic, or cubical Crystals, or White, granular powder.

The drug product is capsules filled with off-white round pellets.

B. Description of How the Drug Product is Intended to be Used

Potassium chloride capsules are used for treatment of Hypokalemia.

The recommended maximum daily dose is 40 to 100 mEq (3.0 to 7.5 g).

C. Basis for Approvability or Not-Approval Recommendation

Upon review of this ANDA, some minor deficiencies were identified and the firm should address these deficiencies.

III. Administrative

A. Reviewer's Signature

Yusuf Amin

B. Endorsements:

HFD-623 Yusuf Amin/Chemist/03/08/05 5/3/05

HFD-623 R. Bykadi, Ph.D./Acting Team Leader/ 5-3-05

HFD-617 Simon Eng/Project Manager/ 5/3/05

C. CC:

ANDA: 77-419

DIV FILE

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10 pages have been withheld as b4 (CCI/TS) immediately following this page

cc: ANDA 77-419
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-623 /Y.Amin/03/23/2005 5/3/05
HFD-623 /R. Bykadi, Ph.D. /3/23/05 5-3-05
HFD-617 /S. Eng, PM /5/2/05 5/3/05

F/T by : ard/5/2/05

V:\FIRMSAM\ANDRX\LTRS&REV\77419.REV1.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-419

BIOEQUIVALENCE REVIEWS

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 77-419	SPONSOR: Andrx Pharmaceuticals
DRUG AND DOSAGE FORM:	Potassium Chloride Extended-release Capsules, USP
STRENGTH(S):	8 mEq and 10 mEq
TYPES OF STUDIES:	Fasting Bioequivalence Study
CLINICAL STUDY SITE:	Algorithme Pharma Inc., Montreal, Canada
ANALYTICAL SITE:	(b) (4)
STUDY SUMMARY:	Fasting BE Study is acceptable
DISSOLUTION:	Acceptable (USP Method), waiver is granted for the 8 mEq strength.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __No_ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable: Yes _X_

PRIMARY REVIEWER: Patrick E. Nwakama BRANCH: III

INITIAL: PEN DATE: 3/13/06

TEAM LEADER: Moheb H. Makary BRANCH: I

INITIAL: MHM DATE: 3/13/06

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL: DPC **DATE:** 3/14/06

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77419 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Potassium Chloride ER Capsules USP, 8 mEq and 10 mEq

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have accepted to conduct dissolution testing as specified in USP 29.

Please note that the bioequivalence comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 77419
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Nwakama

Endorsements: (Draft and Final with Dates)
HFD-658/ P. Nwakama 3/13/06
HFD-658/ M. Makary
HFD-650/ S. Mazzella
HFD-650/ D. Conner 3/14/06

Final: 3/13/2006

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BIOEQUIVALENCE – Acceptable

Submission Date: February 16, 2006

1. **STUDY AMENDMENT** (STA)

Strengths: 8 mEq & 10 mEq
Outcome: AC

Outcome Decisions:
AC – Acceptable

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-419
Drug Product Name	Potassium Chloride Extended-release Capsules, USP
Strength	8 mEq and 10 mEq
Applicant Name	Andrx Pharmaceuticals
Address	4955 Orange Drive, Fort Lauderdale, Florida 33314
Submission Date(s)	February 16, 2006
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	No
File Location	V:\firmsam\Andrx\ltrs&rev\77419a0206.doc

I. Executive Summary

This is a review of a study amendment. The firm has submitted its responses to the DBE's deficiency letter of January 27, 2006. The firm has satisfactorily responded to the following DBE deficiency comments:

1) Please explain how feasible it was to use a single dilution factor of 6493.5 for all the study samples.

2) In the statistical report (page 724) of your submission, you stated that the values of Ae0-24 and Ae0-48 were "obtained by inspection". Please explain how these values could be obtained by inspection.

3) As stated in the clinical report (page 1042) of your submission, the urine volume was recorded via weight at the end of each collection interval. In Tables 5-8 (pages 738-741), the urine volume was listed in liters. Please explain, with example, how the urine volume was converted from "grams" to "liters" for each collected study sample.

The fasting bioequivalence study on the 10 mEq tablet is acceptable. The waiver request for the 8 mEq is granted. The application is now acceptable with no deficiencies.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Potassium Chloride Extended-release Capsules, USP
Reference Product	Micro K® 10 EXTENCAPS® Capsules (also available as 8 mEq capsules)
RLD Manufacturer	KV Pharmaceutical
NDA No.	018238
RLD Approval Date	05/14/84
Indication	Prevention and treatment of Hypokalemia

B. PK/PD Information

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

The current submission provides the firm's responses to DBE deficiency comments (1/27/2006):

Deficiency Comment #1: *Please explain how feasible it was to use a single dilution factor of 6493.5 for all the study samples.*

Firm's Response: Andrx indicated that it demonstrated the "ability to dilute" up to a factor of 6493.5 during the method validation for the analysis of potassium chloride in human urine by atomic absorption. The firm concurred with DBE that had dilution factor of 6493.5 been used for all study samples, final concentrations of some urine samples would have fell outside the low limit of the standard curve. However, during the actual analysis of the subject samples, a lesser dilution factor (< 6493.5) was used to ensure that final concentrations were within the validated range. The actual dilution factor used in the individual run reports is provided in Appendix 2 of this submission. To ensure that the dilution of subject samples was executed correctly, QC samples were also diluted.

In summary, the dilution factor of 6493.5 was the highest value test and established as acceptable in the 'ability to dilute' in the validation study. It was not the dilution factor used in the subject sample analysis. Rather, the study samples were diluted with dilution factor ranging from 472.6 to 3086.4 and the same dilution factor selected for the study sample was also performed on the QC samples.

DBE'S Comment: The firm response is acceptable.

Deficiency Comment #2: *In the statistical report (page 724) of your submission, you stated that the values of Ae0-24 and Ae0-48 were "obtained by inspection". Please explain how these values could be obtained by inspection.*

Firm's Response: The firm stated that the intended meaning of "obtained by inspection" was "obtained by inspection of the data". However, a more definitive description would be:

Ae0-24 and Ae0-48 values were "calculated by summation" of the urinary excretion amount from 0-24 hours and 0-48 hours, respectively.

DBE'S Comment: The firm response is acceptable.

Deficiency Comment #3: *As stated in the clinical report (page 1042) of your submission, the urine volume was recorded via weight at the end of each collection interval. In Tables 5-8 (pages 738-741), the urine volume was listed in liters. Please explain, with example, how the urine volume was converted from "grams" to "liters" for each collected study sample.*

Firm's Response: The firm used '1 g = 1 mL' as conversion factor for the specific gravity of urine since individual subject fluid intake was constant (500 mL water consumed at 0800 hour daily and $\geq$ 200 mL/hour for 12 hours). The firm believed that the 1:1 conversion factor was valid since the amount of total fluid consumed should result in very dilute urine for a low specific gravity. The weight of urine (g) per collection interval is obtained by subtracting the container weight (g) and expressed as volume (mL). The obtained weight of urine (mL) was converted to liters (L) by dividing by 1000.

DBE'S Comment: The firm's response is acceptable.

C. In Vivo Study

See reviews (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc and 77419a0805.doc)

D. Formulation

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

E. In Vitro Dissolution

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

F. Waiver Request (s)

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

G. Deficiency Comments

None

H. Recommendations

1. The bioequivalence study conducted under fasting conditions by Andrx Pharmaceuticals, Inc. on its test product, Potassium Chloride ER capsules, USP 10 mEq, lot #560R020, comparing it to Micro K® 10 mEq capsules, lot #50167, manufactured by KV Pharmaceuticals is acceptable.

2. The dissolution testing conducted by the firm on its Potassium Chloride ER 8 mEq and 10 mEq capsules is complete. The formulation for the 8 mEq is proportionally similar to the 10 mEq strength test product which underwent bioequivalence testing. The waiver request for the 8 mEq capsules of the test product is granted.

3. The dissolution testing should be conducted as specified in USP 29.

From the bioequivalence standpoint, the application is complete.

3/13/06

Patrick Nwakama, Pharm.D. Review Team III, Date

Moheb H. Makary 3/13/06

Moheb H. Makary, Ph.D. Review Team I Date
Team Leader

3/14/06

Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77419 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Potassium Chloride ER Capsules USP, 8 mEq and 10 mEq

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have accepted to conduct dissolution testing as specified in USP 29.

Please note that the bioequivalence comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

In future applications, please include the address of the laboratories conducting the dissolution testing in the bioequivalence section of the ANDA.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-419
Drug Product Name	Potassium Chloride Extended-release Capsules, USP
Strength	8 mEq and 10 mEq
Applicant Name	Andrx Pharmaceuticals
Address	4955 Orange Drive, Fort Lauderdale, Florida 33314
Submission Date(s)	August 16, 2005
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	No
File Location	V:\firmsam\Andrx\ltrs&rev\77419a0805.doc

I. Executive Summary

This is a review of a study amendment. The firm previously submitted (12/1/2004) an in vivo bioequivalence fasting study on the 10 mEq, a biowaiver request for the 8 mEq strength and dissolution data on both strengths. The application was found incomplete because the firm did not submit adequate urinary potassium concentration and excretion data for full statistical analysis (see deficiency comments).

The formulation of the 8 mEq capsule is proportionally similar to the 10 mEq capsule which underwent *in vivo* bioequivalence testing. The dissolution testing using the USP method was acceptable. The DBE concurred with the firm's use of the USP method and specification (900 mL, Water, Basket, 100 rpm; NMT 35% (Q) in 2 hours] in its dissolution testing. However, the waiver cannot be granted at that time because of the deficiency comments in the fasting study.

In this amendment, the firm has submitted the baseline-corrected data based on the average of individual time intervals from two baseline days. In the original submission, baseline adjustment was based on the average of Ae0-24h from two baseline days according to newly issued (October 2005) Guidance on Potassium Chloride Modified-Release Tablets and Capsules. Therefore, the firm's originally submitted data was acceptable for bioequivalence review. Statistical analysis of the urinary pharmacokinetic data for potassium chloride demonstrates bioequivalence. The results of urinary pharmacokinetic data (point estimate, 90% CI) are: ***baseline-uncorrected*** LAe0-24h of 1.01, 96.89 – 104.98%, LAe0-48h of 1.00, 97.25 - 102.69% and LRmax of 0.95, 91.20 – 99.88%; ***baseline-corrected*** LAe0-24h of 0.97, 81.23 – 116.31%, LAe0-48h of 0.98, 91.68 - 104.49% and LRmax of 0.92, 82.50 – 103.33%.

However, the fasting BE study is incomplete. The application is incomplete. Therefore, the waiver request for the 8 mEq can not be granted at this time.

II. Table of Contents

Current Submission:

DBE DEFICIENCY COMMENTS (07/26/2005):

Deficiency Comment #1:

*Please provide complete sets of individual data for the **baseline-corrected**: a) Urinary Potassium Excretion (mEq) per Collection Interval; b) Urinary Potassium Excretion Rate (mEq/hr) per Collection Interval; and c) Urinary Potassium Concentration (mEq/L) per Collection Interval in SAS transport format.*

The bioequivalence data to be submitted should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

a. SUBJ SEQ PER TRT AE24 AE48 RMAX TMAX LAE24 LAE48 LRMAX
b. SUBJ SEQ PER TRT C1 C2 C3 ..... . Cn

Where 'C' is urinary potassium concentration.

Please separate each field with a blank space and indicate missing values with a period (.).

FIRM'S RESPONSE:

The firm has calculated and submitted the FDA requested baseline-corrected (per collection interval) data for urinary potassium 1) amount excretion (mEq), 2) concentration (mEq/L); 3) excretion rate (mEq/h) in SAS transport format. The calculations involved subtracting the pre-dose baseline intervals from respective corresponding post-dose intervals for the excretion amounts, concentrations, and rates. For instance, the - 48 h to - 47 h value was subtracted for the post-dose 0-1 h value, the - 47 h to - 46 h value was subtracted for the post-dose 1-2 h value, and so on. The firm added that the method recommended by the DBE is different from the one presented at the March 2003 FDA Advisory Committee. Citing slide #9 of the FDA presentation, the firm claimed that baseline-correction (based on the average of the two baseline days) using intervals should be applied to only excretion rate (Rmax) and not to the excretion amount (Ae) and excretion concentration. Therefore, as reported in the original submission the firm subtracted the average Ae(0-24) values of the two baseline days (-48h to - 24h and - 24h to 0 h) from the respective post-dose Ae(0-24) values for baseline-corrected calculations of Ae(0-24). For Rmax, the baseline correction calculation was based on the average of the respective collection intervals for the two baseline days to subtract from the post-dose concentrations, for example, the mean excretion rate of -48h to -47h and -24h to -23h was subtracted for the post-dose 0-1 h.

DBE'S COMMENTS:

The firm's baseline correction procedure in the original submission is same as the one contained in the October 2005 CDER Guidance on Potassium Chloride Modified Release Tablets and Capsules. Therefore, the procedure used in the original ANDA is acceptable.

Deficiency Comment #2:

The observed urine concentrations, as you reported, ranged from 7.64 mEq/L to 125 mEq/L (approximately 298 – 4875 mg/L) for the test product and from 9.44 mEq/L to 153 mEq/L (approximately 368 – 5969 mg/L) for the reference product and the standard curve was validated over the concentration range from 0.5 to 2 mg/L. You also reported that the quality control samples were prepared at 45.7 mEq/L, 120 mEq/L, and 240 mEq/L and these quality control samples were diluted using the same dilution factor as that applied to the study samples. You should report the dilution factor used for the study samples. If the dilution factor is different from the 6493.5-fold used in your "ability to dilute" study, you should provide data to support that the dilution procedure is validated.

FIRM'S RESPONSE:

The study samples in each analytical batch and one QC level (QC E) in the analytical run were diluted using the same dilution factor. For the study sample data to be accepted (b) (4) of the QCs per dilution ratio must be with the acceptable range (± (b) (4) %). The firm has provided individual run report in this submission.

DBE's COMMENTS

The firm's response is incomplete. Based on the final concentrations of the urine samples reported, one would conclude that many of study samples would have been outside the lower limit of the standard curve. The firm needs to clarify how it is feasible to use a single dilution factor of 6493.5 for all the study samples.

Deficiency Comment #3:

Please provide justification for using 500 mL Water for administration of the study drugs instead of the 240 mL recommended by the Agency.

FIRM'S RESPONSE:

Per the 2002 FDA Guidance on Potassium Chloride modified-release tablets and capsules, 500 mL water is recommended for administration of the dose. Since the administered dose comprise 8 large capsules, the standard 240 mL of water would not be sufficient for administration. Moreover, since urine was the biological matrix, fluid intake was maintained at 3-5 L/day to ensure adequate rate of urine flow throughout the study period as recommended by the guidance.

DBE's COMMENTS

The firm has satisfactorily responded to the deficiency comment.

III. Submission Summary

A. Drug Product Information

Test Product	Potassium Chloride Extended-release Capsules, USP
Reference Product	Micro K® 10 EXTENCAPS® Capsules (also available as 8 mEq capsules)
RLD Manufacturer	KV Pharmaceutical
NDA No.	018238
RLD Approval Date	05/14/84
Indication	Prevention and treatment of Hypokalemia

B. PK/PD Information

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

Relevant OGD or DBE History

There are four approved ANDAs (#070980, KV; #18238, KV; #73532, Teva and #073531, Teva). KV Pharmaceuticals has two 10 mEq strengths currently available commercially and NDA 18-238 is the RLD.

There are several controlled documents on the drug product potassium.

The current DBE recommendations to establish BE of Potassium Chloride ER Capsules, USP:

- Conduct single-dose *in vivo* fasting BE study on the 10 mEq strength;
- Measure urine concentrations of potassium;
- The 8 mEq strength may be eligible for a biowaiver provided its formulation is proportionally similar and dissolution profile is comparable to the 10 mEq that underwent an acceptable in vivo bioequivalence testing;
- Use the current USP dissolution method and specification:

  Medium: Water
  Volume: 900 mL
  Apparatus: I (Basket)
  Rotational Speed: 100 rpm
  Sampling Times: 10, 15, 30, and 45 minutes
  Specifications: NMT 35% (Q) is dissolved in 2 hours

Agency Guidance

2005 CDER Guidance for Industry: Potassium Chloride Modified Release Tablets and Capsules: In-Vivo Bioequivalence and In-Vitro Dissolution Testing".

Drug Specific Issues (if any)

In response to OGD# 03-328 (Algorithme), the DBE provided the following comments:

1) If the baseline-corrected rate of excretion or amount excreted at a particular time interval is negative, the value should be set to zero.

2) It is recommended that baseline excretion of potassium (obtained during the baseline days) 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.

The following information on urine potassium 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 0-24h (Ae0-24h) and maximal rate of urinary excretion data (Rmax). The two one-sided tests procedure can be used to determine 90 percent confidence intervals.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	
Single-dose fed	No	
In vitro dissolution	No	
Waiver requests	No	
Amendments	Yes	1

D. In Vivo Study

1. Single-dose Fasting Bioequivalence Study

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

Submitted in the Original ANDA

Baseline-uncorrected Results		
Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
Ae0-24h	1.01	96.89 – 104.98
Ae0-48h	1.00	97.25 – 102.69
R_{max}	0.95	91.20 – 99.88

Baseline-corrected Results		
Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
LAe0-24h	0.97	81.23 – 116.3
LAe0-48h	0.98	91.68 – 104.49
LR_{max}	0.92	82.5 – 103.3

Submitted in the Amendment

Baseline-corrected Results		
Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
Ae0-24h	0.99	76.66 – 128.08
Ae0-48h	0.93	64.84 – 134.43
R_{max}	0.93	85.78 – 100.75

Reviewer's Note: The procedure for adjusting baseline potassium concentrations in the original submission was based on the average of Ae0-24h from two baseline days (vs. the average of individual time intervals from two baseline days as was applied in the Amendment). This method is the same as that described in the October 2005 CDER Guidance for modified-release Potassium Chloride. Therefore, only the results from the data contained in the original submission were used to assess bioequivalence of this test product. The baseline correction performed and submitted in the amendment is not necessary.

E. Formulation

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

F. In Vitro Dissolution

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

G. Waiver Request (s)

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

H. Deficiency Comments

1. In the statistical report (page 724), the firm stated that the values of Ae0-24 and Ae0-48 were "obtained by inspection". The firm should clarify how these values can be obtained by inspection.

2. As stated in the clinical report (page 1042), the urine volume was recorded via weight at the end of each collection interval. In Tables 5-8 (pages 738-741), the urine volume was listed in liters. The firm should clarify, with example, how to convert the urine volume in "grams" to "liters" for each study sample collected.

I. Recommendations

1. The bioequivalence study conducted under fasting conditions by Andrx Pharmaceuticals, Inc. on its test product, Potassium Chloride ER capsules, USP 10 mEq, lot #560R020 comparing it to Micro K® 10 mEq capsules, lot #50167 manufactured by KV Pharmaceuticals is incomplete.

2. The formulation for the 8 mEq is proportionally similar to the 10 mEq strength test product which underwent bioequivalence testing. The waiver request for the 8 mEq capsules of the test product can not granted at this time due to the deficiency in the fasting BE study on the 10 mEq capsules.

3. The dissolution testing conducted by the firm on its Potassium Chloride ER 8 mEq capsules is complete. The dissolution testing should be conducted in 900 ml of water at 37°C using USP apparatus I (Basket) at 100 rpm. The test product should meet the following specification:

   Not more than 35% (Q) of the labeled amount of the drug in the dosage form is dissolved in 2 hours.

From the bioequivalence standpoint, the application is incomplete.

1/18/2006

Patrick Nwakama, Pharm.D. Review Team III, Date

1/18/2006

Yih-Chain Huang, Ph.D. Review Team III Date
Team Leader

1/18/06

Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

a) Pharmacokinetic Results

Table 1 Arithmetic Mean Pharmacokinetic Parameters, n=36

Data Submitted in the Original ANDA

Baseline Uncorrected					
	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AE0TO24	146.25	12.80	144.86	12.41	1.01
AE0TO48	281.57	12.41	281.38	11.52	1.00
RMAX	12.43	12.36	13.10	17.29	0.95
TMAX	16.94	70.13	19.06	69.71	0.89
LAE0TO24	144.97	0.10	143.74	0.09	1.01
LAE0TO48	279.25	0.05	279.44	0.04	1.00
LRMAX	12.34	0.98	12.93	1.27	0.95

Baseline Corrected					
	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AE0TO24	42.93	40.05	43.79	32.40	0.98
AE0TO48	178.24	17.05	181.34	15.64	0.98
RMAX	6.75	29.87	7.46	36.92	0.90
LAE0TO24	40.78	1.21	41.60	0.79	0.98
LAE0TO48	175.24	0.11	179.04	0.09	0.98
LRMAX	6.50	4.24	7.04	4.84	0.92

Data Submitted in the Amendment

Baseline Uncorrected					
	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AE0TO24	146.25	12.80	144.86	12.41	1.01
AE0TO48	281.57	12.41	281.38	11.52	1.00
RMAX	12.43	12.36	13.10	17.29	0.95
TMAX	16.94	70.13	19.06	69.71	0.89
LAE0TO24	144.97	0.10	143.74	0.09	1.01
LAE0TO48	279.25	0.05	279.44	0.04	1.00
LRMAX	12.34	0.98	12.93	1.27	0.95

Baseline Corrected					
	Test		Reference		
PARAMETER	Mean	%CV	Mean	%CV	T/R
AE0TO24	84.46	53.2	91.30	50.41	0.92
AE0TO48	127.24	56.8	143.27	53.2	0.89
RMAX	7.28	26.3	8.00	35.2	0.91

UNIT: Ae0-24h and **Ae0-48h** (cumulative urinary excretion) = mEq; **Rmax** (maximal rate of urinary excretion) = mEq/hr

Table 2 Least Square Geometric Means and 90% Confidence Intervals

Data Submitted in the Original ANDA:

Baseline Uncorrected					
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AE0TO24	146.25	144.86	1.01	97.04	104.88
AE0TO48	281.57	281.38	1.00	97.46	102.67
RMAX	12.43	13.10	0.95	89.98	99.70
LAE0TO24	144.97	143.74	1.01	96.89	104.98
LAE0TO48	279.25	279.44	1.00	97.25	102.69
LRMAX	12.34	12.93	0.95	91.20	99.88

Baseline Corrected					
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AE0TO24	42.93	43.79	0.98	83.57	112.52
AE0TO48	178.24	181.34	0.98	92.23	104.36
RMAX	6.75	7.46	0.90	78.31	102.63
LAE0TO24	40.44	41.60	0.97	81.23	116.31
LAE0TO48	175.24	179.04	0.98	91.68	104.49
LRMAX	6.50	7.04	0.92	82.50	103.33

Data Submitted in the Amendment:

Baseline Uncorrected					
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AE0TO24	146.25	144.86	1.01	97.04	104.88
AE0TO48	281.57	281.38	1.00	97.46	102.67
RMAX	12.43	13.10	0.95	89.98	99.70
LAE0TO24	144.97	143.74	1.01	96.89	104.98
LAE0TO48	279.25	279.44	1.00	97.25	102.69
LRMAX	12.34	12.93	0.95	91.20	99.88

Baseline Corrected					
Parameter	Test	Ref.	T/R	LOWCI	UPPCI
LAE0TO24	76.17	76.86	0.99	76.66	128.08
LAE0TO48	111.83	119.78	0.93	64.84	134.43
LRMAX	7.05	7.58	0.93	85.78	100.75

UNIT: Ae0-24h and **Ae0-48h** (cumulative urinary excretion) = mEq; **Rmax** (maximal rate of urinary excretion) = mEq/hr

Table 3 Additional Study Information

	Baseline-uncorrected	Baseline-corrected
Root mean square error, Ae0-24h	0.1007	0.4499
Root mean square error, Ae0-48h	0.0684	0.1641
Root mean square error, R_{max}	0.1140	0.2824
R_{max} and Ae0-24h determined for how many subjects?	All	
Do you agree or disagree with firm's decision?	Yes	
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	All (baseline correction)	
Were the subjects dosed as more than one group?	No	

Table 4: Arithmetic Mean Amount of Urinary Potassium Excretion (mEq)

Baseline Uncorrected

Time (hr)	Mid-point (hr)	Test =T Amount (mEq)	CV	Cum. Amt-T	Reference=R Amount (mEq)	CV	Cum. Amt-R	Amount T/R Ratio	Cum Amt. T/R Ratio
0-1	0.5	3.96	38.24	3.96	3.98	49.48	3.98	0.99	0.99
1-2	1.5	8.46	24.64	12.42	8.51	31.29	12.49	0.99	0.99
2-4	3.0	21.36	20.90	33.78	21.31	20.96	33.80	1.00	1.00
4-6	5.0	18.65	18.20	52.43	19.01	22.4	52.81	0.98	0.99
6-8	7.0	15.47	22.97	67.90	14.19	30.93	67.00	1.09	1.01
8-12	10.0	22.47	24.24	90.36	23.3	31.28	90.30	0.96	1.00
12-16	14.0	34.79	31.64	125.15	33.18	28.2	123.48	1.05	1.01
16-24	20.0	22.07	30.20	147.22	21.77	27.47	145.25	1.01	1.01
24-25	24.5	5.90	37.58	153.12	6.14	46.43	151.39	0.96	1.01
25-26	25.5	6.14	39.82	159.25	6.38	26.33	157.77	0.96	1.01
26-28	27.0	17.62	31.56	172.92	17.62	33.66	171.41	1.00	1.01
28-30	29.0	19.89	28.71	184.35	19.33	27.92	182.23	1.03	1.01
30-32	31.0	18.79	28.77	181.79	20.21	36.73	181.13	0.93	1.00
32-36	34.0	28.04	25.66	191.18	24.28	38.87	186.40	1.15	1.03
36-40	38.0	22.88	34.24	198.58	27.88	36.35	200.09	0.82	0.99
40-48	44.0	16.05	38.43	192.17	14.69	52.84	191.48	1.09	1.00

Table 5: Arithmetic Mean Rate of Urinary Potassium Excretion (mEq/hr)

		Baseline Uncorrected				
Time (hr)	Mid-point (hr)	Test =T Rate-T (mEq/hr)	CV	Reference=R Rate-R, (mEq/hr)	CV	T/R Ratio
0-1	0.5	3.96	38.24	3.98	49.48	0.99
1-2	1.5	8.46	24.64	8.51	31.29	0.99
2-4	3.0	10.68	20.90	10.65	20.96	1.00
4-6	5.0	9.33	18.20	9.51	22.40	0.98
6-8	7.0	7.73	22.97	7.10	30.92	1.09
8-12	10.0	5.62	24.24	5.83	31.27	0.96
12-16	14.0	8.70	31.64	8.30	28.20	1.05
16-24	20.0	2.76	30.20	2.72	27.47	1.01
24-25	24.5	5.90	37.58	6.14	46.43	0.96
25-26	25.5	6.14	39.82	6.38	26.33	0.96
26-28	27.0	8.81	31.56	8.81	33.66	1.00
28-30	29.0	9.95	28.71	9.66	27.92	1.03
30-32	31.0	9.40	28.77	10.11	36.73	0.93
32-36	34.0	7.01	25.66	6.07	38.87	1.15
36-40	38.0	5.72	34.23	6.97	36.34	0.82
40-48	44.0	2.01	38.43	1.84	52.84	1.09

Figure 1: Mean Cumulative Amount of Urinary Potassium Excretion per Interval (mEq),

Baseline-uncorrected

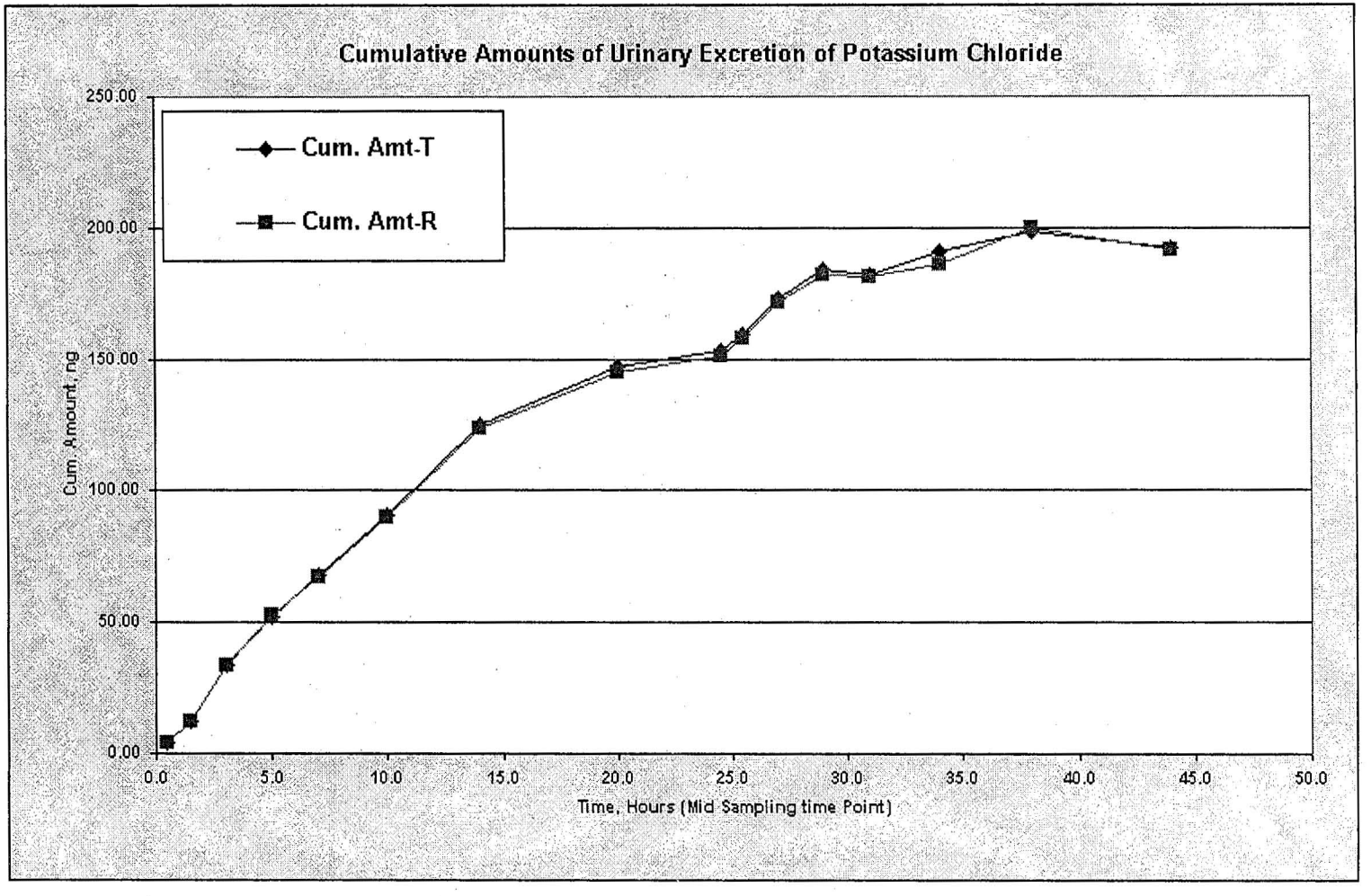
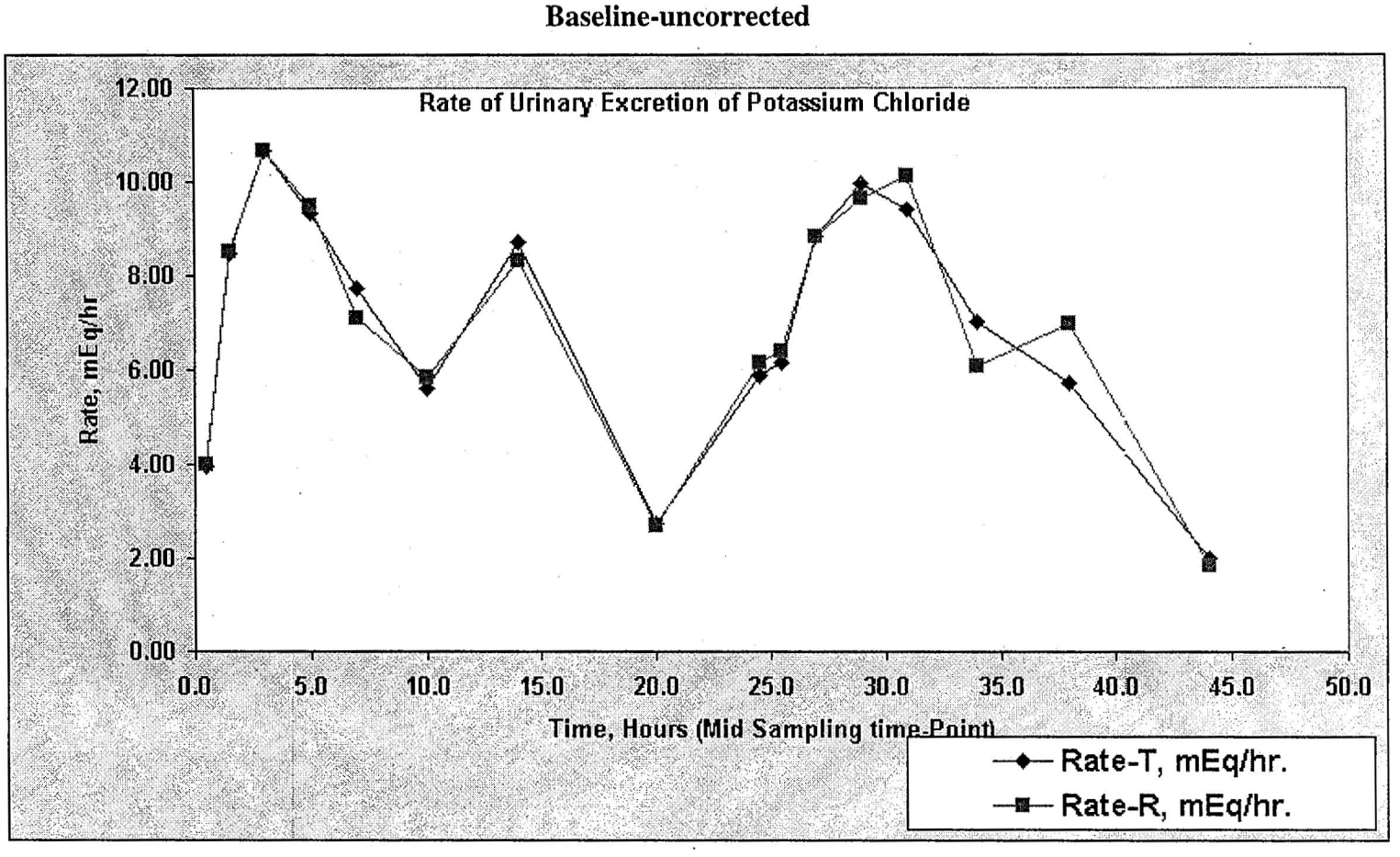


Figure 3: Mean Urinary Potassium Excretion Rate (mEq/hr)



B. Formulation Data

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

C. Dissolution Data

See the original review (V:\firmsam\Andrx\ltrs&rev\77419n1204.doc)

D. Consult Reviews

None

E. SAS Output

Fasting Study	SAS Data	SAS Program	SAS Output
Baseline Uncorrected	 77419POTASBaselineUncorr.xls	 77419POTAS_fast.txt	 77419POTASuncorr_output.txt
Baseline Corrected (original submission)	 77419POTASBaselineCorr.xls		 77419POTAScorr_output.txt
Baseline Corrected (Amendment)	 77419amendPOTASBaselineCorr.xl:		 POTAS77419FDAcorr_output.txt

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 77419 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Potassium Chloride ER Capsules USP, 8 mEq and 10 mEq

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. You stated that you used the same dilution factor of 6493.5 for all study samples. However, based on the final concentrations of the urine samples reported, one would conclude that many of study samples would have been outside the lower limit of the standard curve. Please clarify whether you really used a dilution factor of 6493.5 for all the study samples.

2. In the statistical report (page 724) of your submission, you stated that the values of Ae0-24 and Ae0-48 were "obtained by inspection". Please explain how these values were obtained by inspection.

3. As stated in the clinical report (page 1042) of your submission, the urine volume was recorded via weight at the end of each collection interval. In Tables 5-8(pages 738-741), the urine volume was listed in liters. Please explain, with examples, how the urine volume was converted from "grams" to "liters" for each collected study sample.

Sincerely yours,

Barbara M Davit

for

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 77419
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Nwakama

Endorsements: (Draft and Final with Dates)
HFD-658/ P. Nwakama 1/18/06
HFD-658/ YC Huang 1/18/2006
HFD-650/ S. Mazzella
HFD-650/ D. Conner 1/18/06

Final: 1/18/2006

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BIOEQUIVALENCE – Deficiencies

Submission Date: August 16, 2005

1. **STUDY AMENDMENT** (STA) OIC

Strengths: 8 mEq & 10 mEq
Outcome: IC

Outcome Decisions:
IC – Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	77-419
Drug Product Name	Potassium Chloride Extended-release Capsules, USP
Strength	8 mEq and 10 mEq
Applicant Name	Andrx Pharmaceuticals
Address	4955 Orange Drive, Fort Lauderdale, Florida 33314
Submission Date(s)	December 1, 2004
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	No
File Location	V:\firmsam\Andrx\ltrs&rev\77419N1204.doc

I. Executive Summary

This is a review of an in vivo bioequivalence (BE) study and waiver request only. The dissolution testing had been reviewed separately. This submission contains a fasting BE study on the 10 mEq capsules, a biowaiver request for the 8 mEq capsules and dissolution data on both strengths of the test (Potassium Chloride ER capsules) and the reference listed drug (KV Pharmaceutical's Micro K® / Micro K® 10 EXTENCAPS®) products. This is a two-way, crossover BE study conducted in healthy adult males and females (n = 36). The review of the BE study cannot be completed at this time because the firm did not submit some data (see deficiency comments) necessary for a complete statistical analysis.

The firm requests a waiver of in vivo BE study requirements for the 8 mEq Capsules. The formulation of the 8 mEq capsule is proportionally similar to the 10 mEq capsule which underwent in vivo testing.

The dissolution testing using the USP method was acceptable. The DBE concurred with the firm's use of the USP method and specification (900 mL, Water, Basket, 100 rpm; NMT 35% (Q) in 2 hours] in its dissolution testing. However, the waiver cannot be granted at this time because of the deficiency comments in the fasting study.

The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Potassium Chloride Extended-release Capsules, USP
Reference Product	Micro K® 10 EXTENCAPS® Capsules (also available as 8 mEq capsules)
RLD Manufacturer	KV Pharmaceutical
NDA No.	018238
RLD Approval Date	05/14/84
Indication	Prevention and treatment of Hypokalemia

B. PK/PD Information

(Sources: Electronic Clinical Pharmacology, 2005 PDR and Micromedex)

Bioavailability	Well absorbed
Food Effect	None
Tmax	Not Available
Metabolism	None
Excretion	With normal daily intake from a diet containing about 100 mEq of potassium approximately 85% to 90% is excreted in the urine; 10 – 15% mEq daily excreted.
Half-life	Not applicable
Relevant OGD or DBE History	There are four approved ANDAs (#070980, KV; #18238, KV; #73532, Teva and #073531, Teva). KV Pharmaceuticals has two 10 mEq strengths currently available commercially and NDA 18-238 is the RLD. There are several controlled documents on the drug product potassium. The current DBE recommendations to establish BE of Potassium Chloride ER Capsules, USP: • Conduct single-dose *in vivo* fasting BE study on the 10 mEq strength; • Measure urine concentrations of potassium; • The 8 mEq strength may be eligible for a biowaiver provided its formulation is proportionally similar and dissolution profile is comparable to the 10 mEq that underwent an acceptable in vivo bioequivalence testing; • Use the current USP dissolution method and specification: Medium: Water Volume: 900 mL Apparatus: I (Basket) Rotational Speed: 100 rpm Sampling Times: 10, 15, 30, and 45 minutes Specifications: NMT 35% (Q) is dissolved in 2 hours
Agency Guidance	Guidance for Industry: Potassium Chloride Modified Release Tablets and Capsules: In-Vivo Bioequivalence and In-Vitro Dissolution Testing".

Drug Specific Issues (if any)

In response to OGD# 03-328 (Algorithme), the DBE provided the following comments:

1) If the baseline-corrected rate of excretion or amount excreted at a particular time interval is negative, the value should be set to zero.

2) It is recommended that baseline excretion of potassium (obtained during the baseline days) 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.

The following information on urine potassium 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-24h) and maximal rate of urinary excretion data (Rmax). The two one-sided tests procedure can be used to determine 90 percent confidence intervals.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	Yes	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Vol 1.2, pp. 954 - 968	
	Parent
Analyte name	Potassium
Internal Standard	N/A
Method description	Atomic Absorption Spectroscopy using Flame Ionization
QC range (mg/L)	0.50, 0.90, 1.10, 1.50, and 1.70 mg/L
Standard curve range (mg/L)	0.50, 0.80, 1.00, 1.20, 1.40, 1.60, 1.80 and 2.00 mg/L
Limit of quantitation (mg/L)	0.50 mg/L
Average recovery of Drug (%)	N/A
Average Recovery of Int. Std (%)	N/A
QC Intraday precision range (%CV)	2.0 – 5.3%
QC Intraday accuracy range (%)	99.9 – 103.3%
QC Interday precision range (%CV)	1.5 – 4.3%
QC Interday accuracy range (%)	101.2 – 104.9%
Bench-top stability (hrs)	75 hours
Stock stability (days)	N/A
Processed stability (hrs)	28.6 hours
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	278 days
Dilution integrity (@ 9380 mg/L = 240 mEq/L)	6493.5-fold, 95.6%
Specificity	Baseline endogenous potassium level was determined with a donor since the substance occurs naturally in the urine.
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	R03 - 996
Study Design	Randomized, Single-Dose, two-way Crossover
No. of subjects enrolled	36
No. of subjects completing	36
No. of subjects analyzed	36
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	**Male:** 24 **Female:** 12
Test product	Potassium Chloride ER Capsules
Reference product	Micro-K® 10 Extencaps®
Strength tested	10 mEq
Dose	8 x 10 mEq

Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC0-t	-	-
AUC∞	-	-
Cmax	-	-

(Note: Statistical analyses were not performed because the firm did not provide baseline-corrected data)

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic Repeat	0	0	0	0	0	0	0	0
Above Accepted Range	77	81	3.3	3.5	77	81	3.3	3.5
Incomplete Analysis	66	65	2.9	2.8	66	65	2.9	2.8
Total	**143**	**146**	**6.2**	**6.3**	**143**	**146**	**6.2**	**6.3**

Total No. of Samples = 2304

Did use of recalculated plasma concentration data change study outcome? No (no PK repeats).

F. Formulation

Location in appendix	Section IV.B, Page 15
Are inactive ingredients within IIG limits?	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored?	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test?	N/A
Is the formulation acceptable?	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

See V:\firmsam\Andrx\ltrs&rev\77419D1204.doc

Source of Method	USP
Medium	Water
Volume (mL)	900 ml
USP Apparatus type	I (Basket)
Rotation (rpm)	100 rpm
Firm's proposed specifications	NMT 35% (Q) in 2 hours
FDA-recommended specifications	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	Yes
If not then why?	

H. Waiver Request(s)

Strengths for which waivers are requested	8 mEq
Regulation cited	N/A
Proportional to strength tested in vivo?	Yes (single blend)
Is dissolution acceptable?	Yes
Waivers granted?	No
If not then why?	Deficiency cited for fasting BE study

F2 metric, lower strengths compared to highest strength			
Low strength	**Highest strength**	**F2 metric for test**	**F2 metric for RLD**
8 mEq	10 mEq	90.1	78.6

F2 metric, test compared to reference	
Strength	**F2 metric**
8 mEq	62.0
10 mEq	76.1

I. Deficiency Comments

1. The firm did not submit complete sets of individual **baseline-corrected data**: a) Urinary Potassium Excretion (mEq) per Collection Interval; b) Urinary Potassium Excretion Rate (mEq/hr) per Collection Interval; and c) Urinary Potassium Concentration (mEq/L) per Collection Interval in the SAS transport format.

2. The firm should provide justification for using 500 mL water for administration of the study drugs instead of the 240 mL recommended by the Agency.

3. The observed urine concentrations, as reported by the firm, ranged from 7.64 mEq/L to 125 mEq/L (approximately 298 – 4875 mg/L) for the test product and from 9.44 mEq/L to 153 mEq/L (approximately 368 – 5969 mg/L) for the reference product and the standard curve was validated over the concentration range from 0.5 to 2 mg/L. The firm also reported that the quality control samples were prepared at 45.7 mEq/L, 120 mEq/L, and 240 mEq/L and these quality control samples were

diluted using the same dilution factor as that applied to the study samples. The firm should report the dilution factor used for the study samples. If the dilution factor is different from the 6493.5-fold used in the firm's "ability to dilute" study, the firm should provide data to support that the dilution procedure is validated.

J. Recommendations

1. The bioequivalence study conducted under fasting conditions by Andrx Pharmaceuticals, Inc. on its test product, Potassium Chloride ER capsules, USP 10 mEq, lot #560R020 comparing it to Micro K® 10 mEq capsules, lot #50167 manufactured by KV Pharmaceuticals is incomplete due to the deficiency cited above.

2. The dissolution testing conducted by the firm on its Potassium Chloride ER 8 mEq capsules is complete. The dissolution testing should be conducted in 900 ml of water at 37°C using USP apparatus I (Basket) at 100 rpm. The test product should meet the following specification:

   Not more than 35% (Q) of the labeled amount of the drug in the dosage form is dissolved in 2 hours.

3. The formulation for the 8 mEq is proportionally similar to the 10 mEq strength test product which underwent bioequivalence testing. However, the waiver of in vivo bioequivalence study requirements for the 8 mEq capsules of the test product is denied pending the DBE acceptance of the BE study on the 10 mEq strength capsule.

   Therefore, the application is incomplete.

   The firm should be informed of the recommendations.

7/20/05

Patrick Nwakama, Pharm.D. Review Team III, Date

7/20/2005

Yih-Chain Huang, Ph.D. Review Team III Date
Team Leader

7/21/05

Dale P. Conner, Pharm. D. Date
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information	
Study Number	R03 - 996
Study Title	Randomized, 2-Way Crossover, Bioequivalence Study of Potassium Chloride ER 10 mEq Capsules (Andrx Pharmaceuticals, Inc.) and Micro-K® 10 Extencaps® 10 mEq Capsules (KV Pharmaceuticals) Administered as 8 x 10 mEq Capsules in Healthy Subjects under Fasting Conditions
Clinical Site	PRACS Institute, Ltd., Fargo, North Dakota
Principal Investigator	James D. Carlson, Pharm.D.
Study/Dosing Dates	May 13 - 29, 2004 (dosed on days #7 and #15, respectively).
Analytical Site	(b) (4)
Analytical Director	(b) (4)
Analysis Dates	August 10 – 30, 2004
Storage Period	109 days (Long-term Stability = 278 days)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Potassium Chloride ER	Micro-K® 10 Extencaps®
Manufacturer	Andrx Pharmaceuticals, Inc.	KV Pharmaceutical
Batch/Lot No.	560R020A	50167
Manufacture Date	4/28/04	N/A
Expiration Date	N/A	04/2006
Strength	10 mEq	10 mEq
Dosage Form	Capsules	Capsules
Batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	N/A
Potency	96.8%	100.2%
Content Uniformity (mean, %CV)	96.0% (RSD = 1.0%)	100.6% (RSD = 1.2%)
Formulation	See Appendix Section B	
Dose Administered	8 x 10 mEq	8 x 10 mEq
Route of Administration	Oral (with 500 mL Water)	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	8 days
Randomization Scheme	AB: 2,3,4,5,7,14,15,16,17,20,23,24,25,26,29,30,31,35 BA: 1,6,8,9,10,11,12,13,18,19,21,22,27,28,32,33,34,36
Urine Collection Times	Urine was collected on study Days 5 – 6 and 13 – 14 for baseline (predose) potassium data and on study Days 7 – 8 and 15 – 16 for post-dose potassium data according to the following collection intervals: Pre-dose: 0-8, 8-12, 12-16, 16- 8, 18- 20, 20- 22, 22- 23, 23- 24, 24- 32, 32- 36, 36- 40, 40- 42, 42- 44, 44- 46, 46- 47, 47- 48 h Post-dose: 0-1,1-2, 2-4, 4-6, 6-8, 8- 12, 12- 16, 16- 24, 24 - 25, 25- 26, 26- 28, 28- 30, 30- 32, 32- 36, 36- 40, 40- 48 h.
Urine Volume Collected/Sample	20 ml
Urine Sample Processing/Storage	-20°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Overnight for ≥ 10 hours
Length of Confinement	17 days
Safety Monitoring	Vital signs at baseline (hour 0); and at 12- and 24- h post-dosing of each treatment.

Comments on Study Design: Study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects (n = 36)

Age		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	86.11
Mean	24.9	Mean	159.5	18-40	97.22	Male	66.67	Afr. Amer.	
SD	5.3	SD	23.4	41-64	2.78	Female	33.33	Hispanic	5.56
Range	20 - 40	Range	106 - 207	65-75				Asian	8.33
				>75				Others	

Table 2 Dropout Information

None

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
No treatment-related Adverse events.		

Table 4 Protocol Deviations

Subject #05 took an NSAID on study day #13. The integrity of the study was not compromised.

Comments on Dropouts/Adverse Events/Protocol Deviations:
There were not study drug-related adverse events or major protocol deviations occurred to alter the study outcome.

Bioanalytical Results

Table 5 Assay Quality Control – Within Study

Vol. 1.2, pp. 0946 – 0951, 1014 - 1038	
	Potassium
QC Conc.	0.9, 1.10, 1.50, 1.70 mg/L
Inter day Precision (%CV)	2.4 – 4.3%
Inter day Accuracy (%)	100.6 – 101.8%
Cal. Standards Conc.	0.5, 0.8, 1.0, 1.20, 1.40,1.60, 1.80 & 2.00 mg/L
Inter day Precision (%CV)	0.4 – 0.9%
Inter day Accuracy (%)	99.5 – 100.2%
Linearity Range (range of R^2 values)	0.99984 – 0.99999

Comments on Study Assay Quality Control: See deficiency comments..

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: No interfering peaks

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
DH 8.3	7/06/2002	Clinical Sample Analysis, Selection of Repeats and Data Reporting.

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did use of recalculated plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Study is incomplete (see deficiency comments on page 7).

c) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters, n=36

Mean urine concentrations are presented in Table 11, 12, 13, 14 and Figures 1,2,3,4:

Non-Baseline Adjusted:

	Test		Reference		
Parameter	Mean	%CV	Mean	%CV	T/R
Ae0-24h	-	-	-	-	-
Ae0-48h	-	-	-	-	-
R_{max}	-	-	-	-	-
Tmax	-	-	-	-	-

Baseline Adjusted:

	Test		Reference		
Parameter	Mean	%CV	Mean	%CV	T/R
Ae0-24h	-	-	-	-	-
Ae0-48h	-	-	-	-	-
R_{max}	-	-	-	-	-
Tmax	-	-	-	-	-

UNIT: Ae0-24h = mEq; **Rmax** = mEq/hr; **Tmax** = hr

Table 9 Least Square Geometric Means and 90% Confidence Intervals

Non-Baseline Adjusted:

	Test	Ref.	T/R	LOWCI12	UPPCI12
PARAMETER					
Ae0-24h	-	-	-	-	-
Ae0-48h	-	-	-	-	-
R_{max}	-	-	-	-	
LAe0-24h	-	-	-	-	-
LAe0-48h	-	-	-	-	-
LR_{max}	-	-	-	-	-

Baseline Adjusted:

	Test	Ref.	T/R	LOWCI12	UPPCI12
PARAMETER					
Ae0-24h	-	-	-	-	-
Ae0-48h	-	-	-	-	-
R_{max}	-	-	-	-	-
LAe0-24h	-	-	-	-	-
LAe0-48h	-	-	-	-	-
LR_{max}	-	-	-	-	-

UNIT: Ae0-24h (cumulative urinary excretion) = mEq; **Rmax** (maximal rate of urinary excretion) = mEq/hr

Table 10 Additional Study Information

Root mean square error, Ae0-24h	-
Root mean square error, R_{max}	-
R_{max} and Ae0-24h determined for how many subjects?	-
Do you agree or disagree with firm's decision?	-
Indicate the number of subjects with the following:	
-measurable drug concentrations at 0 hr	All (require baseline correction)
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis:
The firm did not submit complete sets of individual data for the **baseline-corrected:** a) Urinary Potassium Excretion (mEq) per Collection Interval; b) Urinary Potassium Excretion Rate (mEq/hr) per Collection Interval in the SAS transport format.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The single-dose fasting bioequivalence study is incomplete (see deficiency comments on page 7).

Table 11 Mean Urinary Potassium Excretion per Interval (mEq), (Baseline-uncorrected)

Deferred (see deficiency section)

Table 12 Mean Urinary Potassium Excretion per Interval (mEq), (Baseline-corrected)

Deferred (see deficiency section)

Table 13 Mean Rates of Urinary Potassium Excretion (mEq/hr), (Baseline-uncorrected)

Deferred (see deficiency section)

Table 14 Mean Rates of Urinary Potassium Excretion (mEq/hr), (Baseline-corrected)

Deferred (see deficiency section)

Figure 1 Mean Cumulative Amount of Urinary Potassium Excretion per Interval (mEq), (Baseline-uncorrected)

Deferred (see deficiency section)

Figure 2 Mean Cumulative Amount of Urinary Potassium Excretion per Interval (mEq), (Baseline-corrected)

Deferred (see deficiency section)

Figure 3 Mean Rates of Urinary Potassium Excretion (mEq/hr), (Baseline-uncorrected)

Deferred (see deficiency section)

Figure 4 Mean Rates of Urinary Potassium Excretion (mEq/hr), (Baseline-corrected)

Deferred (see deficiency section)

B. Formulation Data

Ingredient	mg / Capsules		% w/w
	8 mEq	10 mEq	
Potassium Chloride, USP	600.00	750.00	(b) (4)
Ethylcellulose, NF		(b) (4)	
Triacetin, USP			
(b) (4)			
Sodium Lauryl Sulfate, NF			
Total Fill Weight			**100.00**
Empty Gelatin Capsules # 00/ Encapsulation			
Total Weight			

(b) (4)

** #00 Capsules, white Opaque Cap and body imprinted with Andrx logo on the cap and "559" on the body in Black Ink. Average weight of empty capsule (b) (4) mg

***#00 Capsules, dark blue Opaque Cap and body imprinted with Andrx logo on the cap and "560" on the body in Black Ink. Average weight of empty capsule (b) (4) mg

- White capsule consist of :

(b) (4)

Blue capsule consists of:

(b) (4)

C. Dissolution Data

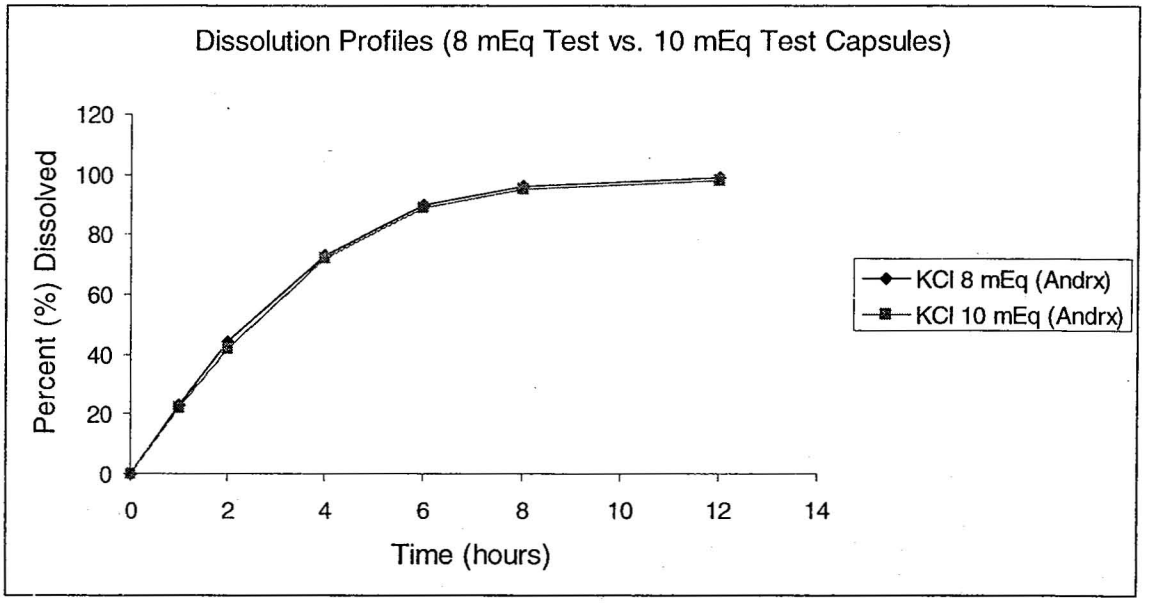
See v:\firmsam\Andrx\ltrs&rev\77419D1204.doc.

USP Method & Specification: 900 mL, Deionized Water, Apparatus I (Basket), 100 rpm; NMT 35% (Q) in 2 hours.

Table 1

Test: Potassium Chloride ER Capsules USP				**Reference: Micro K® Capsules, USP**		
Lot No.:559R020				**Lot No.:030274**		
Strength: 8 mEq				**Strength: 8 mEq**		
No. of Units: 12				No. of Units: 12		
Time(hr)	Mean	Range	%RSD	Mean	Range	%RSD
1	23	20 - 25	8.0	19	18 - 20	4.0
2	44	37 - 47	7.0	37	34 - 39	4.2
4	73	66 - 77	4.3	64	55 - 67	6.0
6	90	85 - 92	2.1	84	81 - 87	2.4
8	96	93 – 98	1.3	93	90 – 97	2.2
12	99	97 - 100	1.0	98	94 – 103	2.5
Test: Potassium Chloride ER Capsules USP				**Reference: Micro K® Capsules, USP**		
Lot No.:560R020				**Lot No.:50167**		
Strength: 10 mEq				**Strength: 10 mEq**		
Time(hr)	Mean	Range	%RSD	Mean	Range	%RSD
1	22	21 – 25	4.9	19	18 – 20	3.4
2	42	41 – 45	2.7	38	36 – 39	2.4
4	72	69 – 74	1.9	69	67 – 70	1.4
6	89	88 – 90	0.8	87	84 – 90	2.1
8	95	94 – 97	1.0	92	86 – 96	2.9
12	98	97 - 99	0.8	99	94 – 102	2.4

Figure 5 Dissolution Profiles



D. Consult Reviews

None

E. SAS Output

Study	SAS Data	SAS Program	SAS Output
Fasting Study	Data Submitted Incomplete		

F. Additional Attachments

None

BIOEQUIVALENCE DEFICIENCY COMMENTS

ANDA: 77419 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT:Potassium Chloride ER Capsules USP,8 mEq and 10 mEq

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please provide complete sets of individual data for the **baseline-corrected**: a) Urinary Potassium Excretion (mEq) per Collection Interval; b) Urinary Potassium Excretion Rate (mEq/hr) per Collection Interval; and c)Urinary Potassium Concentration (mEq/L) per Collection Interval in SAS transport format.

The bioequivalence data to be submitted should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

a. SUBJ SEQ PER TRT AE24 AE48 RMAX TMAX LAE24 LAE48 LRMAX
b. SUBJ SEQ PER TRT C1 C2 C3 ….. . Cn

Where 'C' is urinary potassium concentration.

Please separate each field with a blank space and indicate missing values with a period (.).

2. The observed urine concentrations, as you reported, ranged from 7.64 mEq/L to 125 mEq/L (approximately 298 - 4875 mg/L) for the test product and from 9.44 mEq/L to 153 mEq/L (approximately 368 - 5969 mg/L) for the reference product and the standard curve was validated over the concentration range from 0.5 to 2 mg/L. You also reported that the quality control samples were prepared at 45.7 mEq/L, 120 mEq/L, and 240 mEq/L and these quality control samples were diluted using the same dilution factor as that applied to the study samples. You should report the dilution factor used for the study samples. If the dilution factor is different from the 6493.5-fold used in your "ability to dilute" study, you should provide data to support that the dilution procedure is validated.

3. Please provide justification for using 500 mL Water for administration of the study drugs instead of the 240 mL recommended by the Agency.

Please refer to the Guidance for Industry: "Providing Regulatory Submissions in Electronic Format-ANDAs" for information regarding the proper format at: www.fda.gov/cder/guidance /index.htm (under electronic submissions).

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 77419
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/ P. Nwakama

Endorsements: (Draft and Final with Dates)
HFD-658/ P. Nwakama 7/20/05
HFD-658/ YC Huang 7/20/2005
HFD-650/ S. Mazzella
HFD-650/ D. Conner 7/21/05

Final: 7/20/05

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BIOEQUIVALENCE – Incomplete Submission Date: December 1, 2004

1. **FASTING STUDY** (STF) Strength: 10 mEq
Clinical: Algorithme Pharma Inc., 9000 Boulevard de L'Acadie, Montreal, Canada **Outcome: IC**
Analytical: (b) (4)

2. **DISSOLUTION WAIVER (DIW)** Strength: 8 mEq
Outcome: IC

Outcome Decisions:
IC - Incomplete.

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	77-419
Drug Product Name	Potassium Chloride Extended-Release Capsules, USP
Strength	8 mEq and 10 mEq
Applicant Name	Andrx Pharmaceuticals
Submission Date(s)	December 1, 2004
First Generic	No
Reviewer	Shirley K. Lu
File Location	**V:\firmsam\Andrx\ltrs&rev\77419D1204.doc**
Clinical Site	PRACS Institute, Ltd. Fargo, ND 58104
Analytical Site	(b) (4)
Dissolution Testing Site	**Andrx Pharmaceuticals, Inc.** **4955 Orange Drive** **Fort Lauderdale, FL 33314** **and** **Andrx Pharmaceuticals, Inc.** **2945 West Corporate Lakes Blvd, Suite B** **Weston, FL 33331**

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

The dissolution testing is complete. There is a USP method for this product. The firm's dissolution testing data with the USP method are acceptable. The DBE acknowledges that the firm will follow the USP method and specification. The firm should provide complete SAS transport files of data for the fasting bioequivalence study.

The DBE will review the fasted BE study and waiver request at a later date.

RLD METHOD

Medium	Water
Volume	900 mL
Temperature	37 °C
Apparatus	1 (basket)
Rotational Speed	100 rpm
Specfication	NMT 35% (Q) in 2 hours

Source of Method: USP 28 (as of 4/11/05)

Table 1. Summary of In Vitro Dissolution Data

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)						Study Report Location
					1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	
R03-996	Andrx/ 560R020A	10 mEq ER tab.	Apparatus: **1 (USP)** Speed of Rotation: **100 rpm** Medium: **water** Volume: **900 mL** Temperature: **37°C** Specification: **NMT 35% (Q) in 2 hours**	12	22 (21-25)	42 (41-45)	72 (69-74)	89 (88-90)	95 (94-97)	98 (97-99)	V 1.2 p. 712
R03-996	Micro-K®/ 50167	10 mEq ER tab.		12	19 (18-20)	38 (36-39)	69 (67-70)	87 (84-90)	92 (86-96)	99 (94-102)	
N/A	Andrx/ 559R020A	8 mEq ER tab.		12	23 (20-25)	44 (37-47)	73 (66-77)	90 (85-92)	96 (93-98)	99 (97-100)	N/A
N/A	Micro-K®/ 030274	8 mEq ER tab.		12	19 (18-20)	37 (34-39)	64 (55-67)	84 (81-87)	93 (90-97)	98 (94-103)	

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S1	6	Each unit is within the range Q ± 30%.
S2	6	Average of 12 units (S1 + S2) is within the range between Q - 30% and Q + 35%, and no unit is outside the range Q ± 40%.
S3	12	Average of 24 units (S1 + S2 + S3) is within the range between Q - 30% and Q + 35%, and not more than 2 units are outside the range Q ± 40%.

Table 2. SAS Transport Files

Are the SAS files located in the EDR ? (Yes/No)	
Fasting BE Study	
Plasma Data	No
PK data	No
Fed BE Study	
Plasma Data	N/A
PK Data	N/A

COMMENTS

The dissolution testing is complete. The firm submitted dissolution testing data for their Potassium chloride extended-release capsules, USP, 8 mEq and 10 mEq and Micro-K®, 8 mEq and 10 mEq using the USP method. The USP specification is NMT 35% (Q) in 2 hours. The dissolution data using the USP method indicate that the test products pass the USP specification at the S1 level using the acceptance table specific to this drug product. The firm should provide complete SAS transport files of data for the fasting bioequivalence study.

DEFICIENCY COMMENTS

1. The firm did not submit complete electronic SAS transport files for its bioequivalence (BE) study. The firm should submit data for fasting BE study (R03-996).

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data summary, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

RECOMMENDATIONS:

The *in vitro* dissolution testing conducted by Andrx Pharmaceuticals on its test product, Potassium chloride extended-release capsules, USP, 8 mEq and 10 mEq comparing it to KV Pharmaceutical's Micro-K® capsules, 8 mEq and 10 mEq is complete.

The firm should provide complete SAS transport files of data for the fasting bioequivalence study.

4/14/05

Shirley K. Lu, Ph.D.
Reviewer, Branch IV
Division of Bioequivalence

4/14/2005

Kuldeep R. Dhariwal, Ph.D.
Team Leader, Branch IV
Division of Bioequivalence

4/18/05

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs

V:\firmsam\Andrx\ltrs&rev\77419D1204.doc

CC: ANDA: 77-419
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Drug File
HFD-650/Lu
HFD/650/Fabian-Fritsch

V:\firmsam\Andrx\ltrs&rev\77419D1204.doc

Printed in final on 4/14/05
Endorsements: (Final with Dates)

HFD-650/Lu 4/14/05
HFD-650/Dhariwal 4/14/05
HFD/650/Fabian-Fritsch
HFD-650/Conner 4/18/05

BIOEQUIVALENCE - INCOMPLETE Submission date: December 1, 2004

[NOTE: The *in vitro* testing is incomplete. The fasting BE study and waiver request are pending review]

1. DISSOLUTION (Dissolution Data) Strengths: 8 mEq and 10 mEq

Outcome: IC

Outcome Decisions: IC – Incomplete

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 77-419

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 77-419 Applicant Andrx Pharmaceuticals LLC
Drug Potassium Chloride Extended Release Capsules, USP 8 mEq and 10 mEq Strength(s)

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 20 May 2008 Date 6/1/08
Chief, Reg. Support Branch Initials MHS Initials rlw
Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = _____ NDA# 18-238
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 12/2/2004, BOS=Micro K Capsules NDA 18-238, PI cert. ANDA ack for filing on 12/2/2004 (LO dated 1/25/2005) for both the 8 and 10 mEq strengths. GMP letter issued to the applicant on 7/27/2006. There are no remaining patents or exclusivities which protect the RLD. This ANDA is eligible for Full Approval.

2. Project Manager, Dat Doan Team1 Date 5/15/08 Date _____
Review Support Branch Initials dd Initials _____

Original Rec'd date 12/1/04 EER Status Pending ☐ Acceptable ☐ OAI ☐
Date Acceptable for Filing 12/2/04 Date of EER Status 5/28/08
Patent Certification (type) PI Date of Office Bio Review
Date Patent/Exclus.expires Date of Labeling Approv. Sum 5/26/05
Citizens' Petition/Legal Case Yes ☐ No ☐ Date of Sterility Assur. App.
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☒ MV Commitment Rcd. from Firm Yes ☐ No ☒
Priority Approval Yes ☐ No ☐ Modified-release dosage form: Yes ☒ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise) Interim Dissol. Specs in AP Ltr: Yes ☒
Acceptable Bio review tabbed Yes ☐ No ☐
Bio Review Filed in DFS: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments: BIO AC 3/13/06

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date _____ Date 6/1/08
Name/Initials _____ Name/Initials rlw/for

Comments:
From: Grace, John F
Sent: Friday, May 16, 2008 3:51 PM
To: Barlow, James T; Doan, Dat
Subject: RE: 77-419/Potassium Chloride/Andrx

concur.

From: Barlow, James T

Sent: Friday, May 16, 2008 3:50 PM
To: Doan, Dat; Grace, John F
Subject: RE: 77-419/Potassium Chloride/Andrx

I checked Drugs@FDA,OB and USP.
The labeling Approval Summary signed by John Grace on 5/26/05 remains acceptable.

From: Doan, Dat
Sent: Friday, May 16, 2008 3:37 PM
To: Barlow, James T; Grace, John F
Subject: 77-419/Potassium Chloride/Andrx

Hi Jim, John:

Can I please get your endorsement for 77-419/Potassium Chloride/Andrx?

<< File: 77419.ap.letter.DOC >>
<< File: 77419.ap.labeling.summary.pdf

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 6/1/08
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments: N/A. There are no patents listed in the "Orange Book" for this drug product.

5. Div. Dir./Deputy Dir. Date5/30/08
Chemistry Div. I II OR III Initials PS
Comments:cmc ok, ees ok.

6. Frank Holcombe **First Generics Only** Date 6/1/08
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. TEVA's ANDA 73-531 for this drug product was approved on April 26, 1996.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Micro-K 8 mEq and 10 mEq
KV Pharmaceutical Company NDA 18-238 (001, 002).

8. Peter Rickman Date6/1/08
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐No ☐;Petition: Yes☐ No☐
Comments: Bioequivalence study (fasting) on the 10 mEq capsule strength found acceptable. Waiver granted to the 8 mEq strength under 21 CFr 320.22(d)(2). In-vitro dissolution data for both capsule strengths found acceptable. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 3/14/06.

Final-printed labeling (FPL) found acceptable for approval 5/26/05, as endorsed 5/16/08, above.

CMC found acceptable for approval (Chemistry Review #3) 5/29/08.

OR

8. Robert L. West — Date 6/1/08
Deputy Director, OGD — Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 5/29/08 (Verified 6/1/08). No "OAI" Alerts noted.

There are no patents or exclusivities listed in the current "Orange Book" for this drug product.

With the finding of acceptable cGMP status by the field, this ANDA is recommended for approval.

9. Gary Buehler — Date 6/1/08
Director, OGD — Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Dat Doan — Date6/2/08
Review Support Branch — Initials dd

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
9:25am Time notified of approval by phone
9:30am Time approval letter faxed

FDA Notification:
6/2/08 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
6/2/08 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 018238 Product 002 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through April, 2008
Patent and Generic Drug Product Data Last Updated: May 30, 2008

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dat Doan

6/2/2008 10:41:31 AM

Andrx
PHARMACEUTICALS
LLC

LABELING AMENDMENT

NEW CORRESP

MC

February 14, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
ROCKVILLE MD 20855-2773

ANDA 77-419
Potassium Chloride Extended-release Capsules, 8 mEq & 10 mEq

Dear Sir or Madam:

As per the FDA Docket 92S-0251 (Effective October 31, 2005), Andrx is providing SPL labeling for the above reference application.

Please refer to the enclosed CD, which contains the following file:

- Insert in SPL format.

Please direct any questions regarding this application to William Stahovec at (954) 358-6124, email at wstahovec@andrx.com, or fax at (954) 358-6350.

Sincerely,

William Stahovec
Director of Regulatory Affairs

RECEIVED
FEB 16 2007
OGD / CDER

ANDA 77-419

Andrx Pharmaceuticals, LLC
Attention: Janet Vaughn
Director, Regulatory Affairs
4955 Orange Drive
Fort Lauderdale, FL 33314

JUL 27 2006

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 1, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq.

Reference is also made to your amendments dated May 13, May 20 (two amendments), and August 16, 2005; and February 16, 2006.

The application is deficient and, therefore, not approvable under 21 CFR 314.125 (b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, or holding of Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq comply with current good manufacturing practice (cGMP) regulations.

Our conclusion is based upon apparent systemic violations of cGMP regulations as documented by investigators during multiple inspections of Andrx's manufacturing operations. The most recent inspection concluded in April 2006. Upon review of the investigators' inspectional observations, the Division of Manufacturing and Product Quality in the Center's Office of Compliance recommend that OGD withhold approval of this ANDA until the inspectional deficiencies have been satisfactorily resolved.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the cGMP-related issues have been satisfactorily resolved. Your amendment to the application submitted in response to this not approvable letter will be considered a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to remedy the cGMP problems, and includes a statement from a responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT. Your amendment should be plainly marked as such in your cover letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

RKPatel 7/27/06

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 77-419
ANDA 77-419/DUP
Division File
Field Copy
HFD-324

Endorsements:

HFD-620/ Y. Amin/ S. Han for 7-28-06.
HFD-623/ A. Mueller/ 7/27/06
HFD-617/ S. Eng/ 1/27/2006

V:\FIRMSAM\ANDRX\LTRS&REV\77419.NA.cGMP.ltr.doc
F/T by: SE

NOT APPROVABLE - MINOR

Andrx
PHARMACEUTICALS
LLC

ANDA 77-419
Potassium Chloride Extended-release Capsules, 8 mEq & 10 mEq

February 16, 2006

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AB

RE: BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler:

In accordance with 21 CFR 314.96, Andrx Pharmaceuticals, LLC is submitting a Bioequivalency Amendment to respond to the following deficiencies listed in your January 27, 2006 facsimile for the above-referenced application (facsimile attached):

1. **You stated that you used the same dilution factor of 6493.5 for all study samples. However, based on the final concentrations of the urine samples reported, one would conclude that many of study samples would have been outside the lower limit of the standard curve. Please clarify whether you really used a dilution factor of 6493.5 for all study samples.**

   Response:

   During validation of the method for the analysis of Potassium Chloride in Human Urine by Atomic Absorption, we demonstrated the "ability to dilute" up to a factor of 6493.5. No factor greater than 6493.5 was tested as no need for it was anticipated. (Please see a copy of page 9 appearing in the validation report, added for your convenience and identified here as Appendix 1).

   You are correct in stating that had the dilution factor of 6493.5 been used for all study samples, final concentrations of some urine samples would have been outside the lower limit of the standard curve. However, during the analysis of the subject samples, the dilution factor used was not 6493.5 but rather a smaller dilution factor - one appropriate to ensure that final concentrations fell within the validated range. The actual dilution factor used was provided in the individual run reports submitted, but a copy is attached for your convenience. (Appendix 2).

   To ensure that the dilution of subject samples was carried out correctly, quality control samples were also diluted. The quality control sample, identified as QCE, was diluted using the same dilution factor (for example, 935.2) as was used to dilute the clinical samples. For the dilution result to be acceptable, the results obtained for the Quality Control must meet pre-determined (as per SOP) criteria. (b) (4) Quality Control samples that were diluted must have a final result (once the dilution factor is taken into account) that is within (b) (4)% of the nominal concentration for the study sample data to be accepted and reported.

RECEIVED
FEB 17 2006
OGD / CDER

In Summary: The dilution factor 6493.5 was at the highest value which we tested and established as acceptable in the "ability to dilute" in our validation study only. It was not the dilution factor used in the subject sample analysis.

- Study samples were diluted using a dilution factor varying from 472.6 to 3086.4. The dilution factor chosen ensured that the concentration fell within the validated range.

- The same dilution factor (for example, 472.6) carried out on a batch of clinical samples was applied to quality control samples. (This dilution factor at no time exceeded the highest established dilution factor of 6493.5).

2. **In the statistical report (page 724) of your submission, you stated that the values of Ae0-24 and Ae0-48 were 'obtained by inspection'. Please explain how these values were obtained by inspection**

Response:

The statistical report currently states the following:

Ae0-24: Cumulative urinary excretion from 0-24 hours (mEq), obtained by inspection
Ae0-48: Cumulative urinary excretion from 0-48 hours (mEq), obtained by inspection

The intended meaning of "obtained by inspection" was "obtained by inspection *of the data*". However, a more definitive description would be:

Ae0-24: Cumulative urinary excretion from 0-24 hours (mEq), calculated by summation of the urinary excretion amount from 0-24 hours

Ae0-48: Cumulative urinary excretion from 0-48 hours (mEq), calculated by summation of the urinary excretion amount from 0-48 hours

3. **As stated in the clinical report (page 1042) of your submission, the urine volume was recorded via weight at the end of each collection interval. In Tables 5-8 (pages 738-741), the urine volume was listed in liters. Please explain, with examples, how the urine volume was converted from "grams" to "liters" for each collected study sample.**

Response:

The conversion factor used for the Specific Gravity of urine is such that 1 g is equivalent to 1 mL. Therefore the conversion is 1 g = 1 mL. The use of this conversion factor is considered valid, as the fluid intake of each study subject is constant and consistent as per protocol (Page 10 of protocol - 500 mL of room temperature water will be consumed at approximately 0800 hour each day. At least 200 mL of fluid will be consumed every hour for the next 12 hours.) With similar fluid intake for all subjects (at least 3660 mL in 12 hours), the urine specific gravity for the subjects can therefore be expected to be low (the result of dilute urine), consistent and collectively within a narrow range. Therefore using 1g equals 1 mL as a conversion factor is valid.

Tables 1a – 4a lists the Container and Total Weight (in grams [or mL]). When calculating the volume (Tables 5 - 8), the Container Weight is being subtracted from the Total Weight. This value is then divided by 1000, converting mL to L.

Example using Subject 1, Period 2, -48 to -47h collection interval:
Table 1a:
Individual Container Weight at Each Collection Interval–Test Product (Baseline) is **48.62 g**

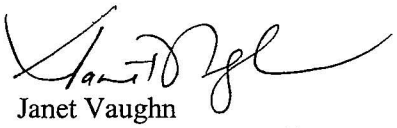
Table 2a:
Individual Container and Urine Weight at Each Collection Interval–Test Product (Baseline) is **94.1 g**

Hence the weight of urine for this interval is 94.1 g – 48.62 g = **45.48 g**, and based on 1 g = 1 mL conversion, becomes **45.48 mL**. This value is then converted to liters by dividing by 1000 and is found in Table 5 Individual Urine Volume at Each Collection Interval – Test Product (Baseline), in liters as **0.045 L** (rounded to three significant figures).

****

Should you have any questions or comments concerning this amendment, please contact the undersigned at (954) 358-6125 *(direct line)*, (954) 214-0145 *(cellular)* or (954) 358-6350 *(Fax.)*.

Sincerely,



Janet Vaughn
Director Regulatory Affairs

BIOEQUIVALENCY AMENDMENT

ANDA 77-419

JAN 27 2006

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Andrx Pharmaceuticals, LLC

TEL: 954-358-6125

ATTN: Janet Vaughn

FAX: 954-358-6350

FROM: Steven Mazzella

PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 16, 2005, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Potassium Chloride Extended Release Capsules USP, 8 mEq and 10 mEq.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 77419 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Potassium Chloride ER Capsules USP, 8 mEq and 10 mEq

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. You stated that you used the same dilution factor of 6493.5 for all study samples. However, based on the final concentrations of the urine samples reported, one would conclude that many of study samples would have been outside the lower limit of the standard curve. Please clarify whether you really used a dilution factor of 6493.5 for all the study samples.

2. In the statistical report (page 724) of your submission, you stated that the values of Ae0-24 and Ae0-48 were "obtained by inspection". Please explain how these values were obtained by inspection.

3. As stated in the clinical report (page 1042) of your submission, the urine volume was recorded via weight at the end of each collection interval. In Tables 5-8(pages 738-741), the urine volume was listed in liters. Please explain, with examples, how the urine volume was converted from "grams" to "liters" for each collected study sample.

Sincerely yours,

Barbara D. Sauvit

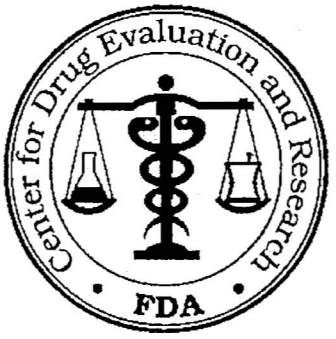
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY AMENDMENT

ANDA 77-419

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

JUL 26 2005



APPLICANT: Andrx Pharmaceuticals, LLC TEL: 954-358-6125

ATTN: Janet Vaughn FAX: 954-358-6350

FROM: Steven Mazzella PROJECT MANAGER: (301) 827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 1, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Potassium Chloride Extended Release Capsules USP, 8 mEq and 10 mEq.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

m

BIOEQUIVALENCE DEFICIENCY COMMENTS

ANDA: 77419 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT:Potassium Chloride ER Capsules USP,8 mEq and 10 mEq

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please provide complete sets of individual data for the **baseline-corrected**: a) Urinary Potassium Excretion (mEq) per Collection Interval; b) Urinary Potassium Excretion Rate (mEq/hr) per Collection Interval; and c)Urinary Potassium Concentration (mEq/L) per Collection Interval in SAS transport format.

The bioequivalence data to be submitted should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

a. SUBJ SEQ PER TRT AE24 AE48 RMAX TMAX LAE24 LAE48 LRMAX
b. SUBJ SEQ PER TRT C1 C2 C3 ….. . Cn

Where 'C' is urinary potassium concentration.

Please separate each field with a blank space and indicate missing values with a period (.).

2. The observed urine concentrations, as you reported, ranged from 7.64 mEq/L to 125 mEq/L (approximately 298 - 4875 mg/L) for the test product and from 9.44 mEq/L to 153 mEq/L (approximately 368 - 5969 mg/L) for the reference product and the standard curve was validated over the concentration range from 0.5 to 2 mg/L. You also reported that the quality control samples were prepared at 45.7 mEq/L, 120 mEq/L, and 240 mEq/L and these quality control samples were diluted using the same dilution factor as that applied to the study samples. You should report the dilution factor used for the study samples. If the dilution factor is different from the 6493.5-fold used in your "ability to dilute" study, you should provide data to support that the dilution procedure is validated.

3. Please provide justification for using 500 mL Water for administration of the study drugs instead of the 240 mL recommended by the Agency.

Please refer to the Guidance for Industry: "Providing Regulatory Submissions in Electronic Format-ANDAs" for information regarding the proper format at: www.fda.gov/cder/guidance /index.htm (under electronic submissions).

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MINOR AMENDMENT

MAY 05 2005

ANDA 77419

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Andrx Pharmaceuticals, LLC

TEL: 954-358-6125

ATTN: Janet Vaughn

FAX: 954-358-6350

FROM: Simon Eng

PROJECT MANAGER: (301) 827-5765

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 1, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided.

5/4/05

MAY 05 2005

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 77-419 APPLICANT: Andrx Pharmaceuticals, LLC

DRUG PRODUCT: Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The fill weight of 8 mEq capsules as per the unit dose composition on p. 0057 is (b) (4) mg. The range should (b) (4) mg. However, your fill target weight for the 8 mEq exhibit batch # 559R020 is (b) (4) mg. Please explain. Please provide the unplanned deviation report mentioned on p. 0371.

2. Please reduce the (b) (4)) specification for the drug product to be more consistent with the reported data.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional Room Temperature stability data accrued to date.

2. The Labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies.

3. The Bioequivalence information which you have provided is under review. After this review is completed, deficiencies, if any, will be communicated to you under a separate cover.

4. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval.

Sincerely yours,

G. Beyka Di

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Andrx
PHARMACEUTICALS
LLC

ANDA 77-419
Potassium Chloride Extended-release Capsules, 8 mEq & 10 mEq

August 16, 2005

ORIG AMENDMENT
N/HAB

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler:

Reference is made to your facsimile dated July 26, 2005 (Bioequivalence Amendment) for the above referenced application (facsimile attached). In accordance with 21 CFR 314.96, Andrx Pharmaceuticals is submitting a complete response to the deficiencies listed in the facsimile.

1. **Please provide complete sets of individual data for the baseline-corrected: a) Urinary Potassium Excretion (mEq) per Collection Interval; b) Urinary Potassium Excretion Rate (mEq/hr) per Collection Interval; and c) Urinary Potassium Concentration (mEq/L) per collection Interval in SAS transport format.**

   The bioequivalence data to be submitted should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

   a. **SUBJ SEQ PER TRT AE24 RMAX TMAX LAE24 LAE48 LRMX**
   b. **SUBJ SEQ PER TRT C1 C2 C3.....Cn**

   Where 'C' is urinary potassium concentration

   Response:

   On the accompanied CD, find supplied the requested information in SAS transport file format, the Individual *Baseline Corrected data* for: a) Urinary Potassium Excretion (mEq) per Collection Interval b) Urinary Potassium Excretion Rate (mEq/hr) per Collection Interval and c) Urinary Potassium Concentration (mEq/L) per Collection Interval, and as requested, the data is supplied in two files. The data is provided electronically and as a hard copy as **Exhibit 1.**

   The calculations of the Urinary Potassium Excretion (mEq), Urinary Potassium Concentration (mEq/L) and Urinary Excretion Rate (mEq/h) baseline-corrected data per collection interval data supplied on the CD involved subtracting the pre-dose baseline intervals from the respective corresponding post-dose intervals for the excretion amounts, concentrations, and rates, for example, the -48h to –47h value was subtracted for the post-dose 0-1 h value, the -47h to –46h value was subtracted for the post-dose 1-2h value, and so on.

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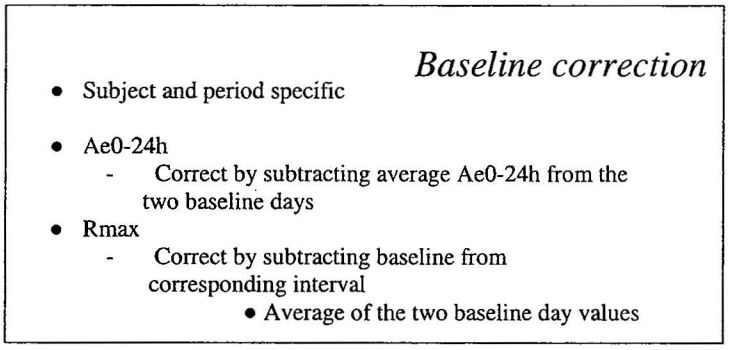
It is important to note the procedure for the baseline-correction calculation used in the Andrx ANDA 77-419 submission differs from the above method. The method of calculations used in the Andrx ANDA submission had been defined by an FDA Advisory Committee presentation[1] since the FDA Guidance[2] was not definitive on the method of baseline-corrected parameter calculation. For convenience, information from that presentation, specifically slide 9, is presented below:



Therefore, it is important to note the baseline-corrected Ae(0-24) (mEq), Ae(0-48) (mEq), concentration (mEq/L) and Rmax (mEq/h) data supplied in the current attached tables, *as calculated per collection interval*, were not included in the original submitted report. The reason is the method used to calculate the baseline-corrected excretion amount (mEq) and excretion concentration (mEq/L) parameters in the original submitted statistical report did not involve subtracting the pre-dose baseline intervals from the respective post-dose intervals.

Instead, as shown in the above slide, it was specified that any baseline-correction using collection intervals should be used for excretion rate (Rmax) calculations *only* (but based on the *average* of the two baseline days) and not excretion amount (Ae, mEq) (nor excretion concentration, mEq/L) calculations. Therefore, in the original submitted statistical report, for baseline-corrected calculations of Ae(0-24), the average Ae(0-24) of the two baseline days (-48h to -24h and -24h to 0h) was subtracted from the respective post-dose Ae(0-24) values.

And although the method used for the calculation of the rate of excretion parameter, Rmax, in the Andrx ANDA submission did utilize the individual collection intervals, the calculation was based on the *average* of the respective collection intervals for the two baseline days to subtract from the post-dose concentrations, for example, the mean excretion rate of –48h to –47h and –24h to –23h was subtracted for the post-dose 0-1 h.

---

[1] Davit, Barbara M. Deputy Director, Division of Bioequivalence, Office of Generic Drugs. Presentation entitled '*Potassium Chloride Tablets & Capsules - Documentation of BE*' before the Advisory Committee for Pharmaceutical Sciences on the meeting topic 'Bioavailability/Bioequivalence of Endogenous Drugs', Mar 13, 2003
Slides: http://www.fda.gov/ohrms/dockets/ac/03/slides/3926S2_08_Davit.ppt;
Transcript: http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T2.pdf

[2] Food and Drug Administration. Draft Guidance for Industry: *Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing.* CDER. August 2002

2. **The observed urine concentrations, as you reported, ranged from 7.64 mEq/L to 125 mEq/L (approximately 298 – 4875 mg/L) for the test product and from 9.44 mEq/L to 153 mEq/L (approximately 369 – 5969 mg/L) for the reference product and the standard curve was validated over the concentration range from 0.5 to 2 mg/L. You also reported that the quality control samples were prepared at 45.7 mEq/L, 120 mEq/L, and 240 mEq/L and these quality control samples were diluted using the same dilution factor as that applied to the study samples. You should report the dilution factor used for the study samples. If the dilution factor is different from the 6493.5-fold used in your 'ability to dilute' study, you should provide data to support that the dilution procedure is validated.**

   Response:

   In each analytical batch the study samples and one (1) QC level, identified as QC E in the analytical run, were diluted using the same dilution factor. (b) (4) QCs per dilution ratio must be within the acceptable range of (+ (b) (4) %), for the study sample data to be accepted and reported. Each individual run report, which includes the dilution factor used for the QC e and study samples, as well as the results of the diluted QC Es and the diluted study is provided as Exhibit 2.

3. **Please provide justification for using 500 mL water for administration of the study drugs instead of the 240 mL recommended by the Agency.**

   Response:

   The protocol design followed the FDA Guidance[3] for this product. For dose administration this document recommended the product should be given by mouth with 500mL of room temperature water. Since the administered dose (80 mEq) was 8 large capsules, the standard 240 mL of water would potentially not be a sufficient amount of fluid for dose administration. In addition, since urine was the biological matrix, fluid intake was maintained at 3,000 to 5,000 mL/day to ensure an adequate rate of urine flow throughout the study period as recommended by the guidance.

Should you have any questions or comments concerning this amendment, please contact the undersigned at (954) 358-6125 *(direct line)*, (954) 214-0145 *(cellular)* or (954) 358-6350 *(Fax.)*.

Sincerely,

Janet Vaughn
Director Regulatory Affairs

---

[3] Food and Drug Administration. Draft Guidance for Industry: *Potassium Chloride Modified-Release Tablets and Capsules: In Vivo Bioequivalence and In Vitro Dissolution Testing.* CDER. August 2002

Andrx
PHARMACEUTICALS
LLC

ANDA 77-419
Potassium Chloride Extended-release Capsules, 8 mEq & 10 mEq

May 20, 2005

ORIG AMENDMENT
N/AB

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: BIOEQUIVALENCY AMENDMENT

Dear Mr. Buehler:

Reference is made to your facsimile dated April 20, 2005 (Bioequivalence Deficiencies) for the above referenced application (facsimile attached). In accordance with 21 CFR 314.96, Andrx Pharmaceuticals is submitting a complete response to the deficiencies listed in the facsimile.

1. **Please submit complete electronic SAS transport files of data for the fasting bioequivalence study (R03-996).**

   Response:
   As requested, we are providing the complete electronic SAS transport files of data for the fasting bioequivalence study (R03-996) as **Exhibit 1**.

2. **In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.**

   Response:
   As requested, we are providing the in-vivo study data, dissolution data and formulation data in the format specified in the template provided. The study summaries in this template are provided in an electronic file as **Exhibit 2**.

3. **The DBE concurs with the use of the following USP method and specification:**

   The dissolution testing should be conducted in 900 mL of water at 37 °C using USP Apparatus 1 (baskets) at 100 rpm.

   Not more than 35% (Q) of the labeled amount of potassium chloride in the dosage form is dissolved in 2 hours.

   Response:
   We acknowledge the DBE concurrence of the above USP method and specifications.

RECEIVED
MAY 24 2005
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Should you have any questions or comments concerning this amendment, please contact the undersigned at (954) 358-6125 *(direct line)*, (954) 214-0145 *(cellular)* or (954) 358-6350 *(Fax.)*.

Sincerely,

Janet Vaughn
Director Regulatory Affairs

Andrx
PHARMACEUTICALS
LLC

ORIG AMENDMENT
N/AF

ANDA #77-419
Potassium Chloride Extended-release Capsules, 8 mEq & 10 mEq

May 20, 2005

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Final Printed Labeling

Dear Mr. Buehler:

Reference is made to the FDA facsimile dated March 17, 2004 (copy attached), which states that the labeling submitted in our original ANDA is satisfactory in draft. Andrx Pharmaceuticals is hereby submitting final printed labeling for the above referenced application. Please be informed that no changes to the labeling have been made since our Original ANDA submitted on December 1, 2004.

In this regard, please find enclosed a hard copy and a compact disk with electronic copies of the final printed labeling for the following in PDF format:

1. Container labels
2. Package Insert

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6125 *(telephone)*, (954) 214-0145 *(cellular)* or (954) 358-6350 *(fax)*.

Sincerely,

Janet Vaughn
Director Regulatory Affairs

RECEIVED
MAY 23 2005
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4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx
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ANDA 77-419
Potassium Chloride Extended-release Capsules, 8 mEq & 10 mEq

May 13, 2005

ORIG AMENDMENT
N/AM

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: MINOR AMENDMENT: CHEMISTRY COMMENTS

Dear Mr. Buehler:

Reference is made to your facsimile dated May 5, 2005 (chemistry comments) for the above referenced application (facsimile attached). In accordance with 21 CFR 314.96, Andrx Pharmaceuticals is submitting a complete response to the deficiencies listed in the facsimile.

Response to Chemistry Comments

A. Deficiencies:

1. **The fill weight of 8 mEq capsules as per the unit dose composition on p. 0057 is (b) (4) mg. The range should be (b) (4) mg. However, your fill target weight for the 8 mEq exhibit batch #559R020 is (b) (4) mg. Please explain. Please provide the unplanned deviation report mentioned on p. 0371.**

Response
The unplanned deviation report mentioned on page 0371 of the original application is provided under **Tab 1**. The theoretical fill weight of the 8 mEq capsules is (b) (4) mg, as indicated in the unit dose composition statement on page 0057. However, to achieve the required labeled amount of active ingredient per capsule, the fill weight is adjusted based on (b) (4)[1]. This adjustment step is provided for in the proposed commercial batch record (page 0187 of the original ANDA) but was not specified in the master batch record at the time the test batch was manufactured, thus necessitating the unplanned deviation report.

2. **Please reduce the (b) (4)) specification for the drug product to be more consistent with the reported data.**

Response
The (b) (4)) specification has been tightened from NMT (b) (4) ppm to NMT (b) (4) ppm. This is well within the ICH recommended limit for (b) (4) (that is, NMT (b) (4) ppm). A copy of the revised drug product release specifications is provided under **Tab 2**.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. **Please provide any additional Room Temperature stability data accrued to date.**

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MAY 16 2005
OGD / CDER

[1] The target fill weight is adjusted if (b) (4)

Response
Additional long-term stability data is provided under **Tab 3**. The data indicates that the product is stable for up to 9 months at room temperature.

2. **The Labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies.**

Response
We note and acknowledge that the labeling portion of the application is currently under review and that the Division of Labeling and Program Support will notify us under separate cover of any labeling deficiencies.

3. **The Bioequivalence information which you have provided is under review. After this review is completed, deficiencies, if any, will be communicated to your under a separate cover.**

Response
We note and acknowledge that our Bioequivalence information is still under review and that after this review is completed, deficiencies, if any, will be communicated to us under separate cover.

4. **All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval.**

Response
We note and acknowledge that all facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval.

****

Andrx Pharmaceuticals certifies that a Field Copy of this amendment was submitted to the Florida District Office. That field copy is a true copy of the information contained in this amendment.

Should you have any questions or comments concerning this amendment, please contact the undersigned at (954) 358-6125 *(direct line)*, (954) 214-0145 *(cellular)* or (954) 358-6350 *(Fax.)*.

Sincerely,

Janet Vaughn
Director Regulatory Affairs

BIOEQUIVALENCE DEFICIENCIES APR 2 0 2005

ANDA: 77-419 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Potassium Chloride Extended-Release Capsules, USP, 8 mEq and 10 mEq

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence study and waiver request will be conducted later. The following deficiencies have been identified:

1. Please submit complete electronic SAS transport files of data for the fasting bioequivalence study (R03-996).

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the in-vivo study data, dissolution data and formulation data in the format specified in the attached template. This template incorporates some elements of the CTD format. We request that you provide the study summaries in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated. It would be helpful if you could provide this information for any other applications pending in the Division and in applications to be submitted in the future.

3. The DBE concurs with the use of the following USP method and specification:

The dissolution testing should be conducted in 900 mL water at 37°C using USP Apparatus 1 (baskets) at 100 rpm.

Not more than 35% (Q) of the labeled amount of potassium chloride in the dosage form is dissolved in 2 hours.

Sincerely yours,

Barbara M Saw. for

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Table 1. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (units/mL)	T_{max} (hr)	AUC_{0-t} (units)	AUC_{∞} (units)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
Study #	Fasting study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean age (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #
Study #	Fed study title	Randomized, single-dose, crossover	Test product, strength, Tab./Cap./Susp., p.o. [Batch #] Ref. product, strength, Tab./Cap./Susp., p.o. [Batch #]	# completing (#M/#F) Healthy subjects or patients mean y (range)	M ± S.D. M ± S.D.	Mn or Md No SD	M ± S.D. M ± S.D.	M ± S.D. M ± S.D.	Mean No SD	Mean No SD	Vol. # p. #

Table 2. Statistical Summary of the Comparative Bioavailability Data

Drug Dose (# x mg) Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t}				
AUC_{∞}				
C_{max}				
Fed Bioequivalence Study				
Parameter	**Test**	**Reference**	**100*Ratio**	**90% C.I.**
AUC_{0-t}				
AUC_{∞}				
C_{max}				

Table 3. Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Provide the volume(s) and page(s)
Analyte	Provide the name(s) of the analyte(s)
Internal standard (IS)	Identify the internal standard used
Method description	Brief description of extraction method; analytical method
Limit of quantitation	LOQ, units
Average recovery of drug (%)	%
Average recovery of IS (%)	%
Standard curve concentrations (units/mL)	Standard curve range and appropriate concentration units
QC concentrations (units/mL)	List all the concentrations used
QC Intraday precision range (%)	Range or per QC
QC Intraday accuracy range (%)	Range or per QC
QC Interday precision range (%)	Range or per QC
QC Interday accuracy range (%)	Range or per QC
Bench-top stability (hrs)	hours @ room temperature
Stock stability (days)	days @ 4°C
Processed stability (hrs)	hours @ room temperature; hours @ 4°C
Freeze-thaw stability (cycles)	# cycles
Long-term storage stability (days)	17 days @ -20°C (or other)
Dilution integrity	Concentration diluted X-fold
Selectivity	No interfering peaks noted in blank plasma samples

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection Times Mean %Dissolved (Range)				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Dissolution: Apparatus Speed of Rotation: rpm Medium: Volume: mL Temperature: °C	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

Table 5. Formulation Data

Ingredient	Amount (mg) / Tablet		Amount (%) Tablet	
	Lower strength	Higher strength	Lower strength	Higher strength
Cores				
Coating				
Total			100.00	100.0

Table 7. Incidence of Adverse Events in Individual Studies

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body as a whole						
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular						
Hypotension						
Etc.						
Gastrointestinal						
Constipation						
Etc.						
Other organ sys.						
Total	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

Table 8. Reanalysis of Study Samples

Study No. Additional information in Volume(s), Page(s)								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]								
Reason A (e.g. below LOQ)								
Reason B								
Reason C								
Etc.								
Total								

[1] If no repeats were performed for pharmacokinetic reasons, insert "0.0" throughout table

ANDA 77-419

Andrx Pharmaceuticals, LLC
Attention: Janet Vaughn
4955 Orange Drive
Fort Lauderdale, FL 33314

JAN 25 2005

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated January 11, 2005 and your correspondence dated January 11, 2005.

NAME OF DRUG: Potassium Chloride Extended-release Capsules USP, 8 mEq and 10 mEq

DATE OF APPLICATION: December 1, 2004

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 2, 2004

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Simon Eng
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 77-419

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB _____ date 24 JAN 2005
HFD-615/ACamphire, CSO _____ 1/11/05 date
Word File
V:\FIRMSAM\Andrx\LTRS&REV\77419.ACK
FT/ January 12, 2005
ANDA Acknowledgment Letter!

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA Nbr: 77-419 **FIRM NAME:** ANDRX PHARMACEUTICALS, LLC

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: POTASSIUM CHLORIDE USP
DOSAGE FORM: CAPSULE, EXTENDED-RELEASE
600 MG EQ TO 8 MG AND 750 MG MG EQ TO 10 MG

Bio Assignments:		Micro Review
☒ BPH	☐ BCE	☐
☐ BST	☒ BDI	

Random Queue: 1
Chem Team Leader: Mueller, Albert PM: Simon Eng Labeling Reviewer: James Barlow

Letter Date: DECEMBER 1, 2004 ✓	**Received Date:** DECEMBER 2, 2004 ✓
Comments: EC - 2 YES **On Cards:** YES **Therapeutic Code:** 1020500 POTASSIUM SALTS	
Archival Format: PAPER **Sections I** **(356H Sections per EDR Email)** **Review copy**: YES E-Media Disposition: YES SENT TO EDR Not applicable to electronic sections Field Copy Certification (Original Signature) YES ✓	
Methods Validation Package (3 copies PAPER archive) **YES** (Required for Non-USP drugs)	
Cover Letter YES	**Table of Contents** YES
PART 3 Combination Product Category N Not a Part3 Combo Product (Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm	

Reviewing CSO/CST Vaughn **Date** 10-Jan-05	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: [signature]	**Date:** 24 JAN 2005
ADDITIONAL COMMENTS REGARDING THE ANDA: Acceptable for filing 11-Jan-05: requested schematic drawing for (b)(4) cc bottle and a revised EIAS (lists old citation)	
Top 200 Drug Product:	

Janet Vaughn
(direct) 954-358-6125
(cell) 954-358-6350

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** YES (Statement regarding Rx/OTC Status) RX YES	☑
Sec. II	**Basis for Submission** **NDA# : 18-238** Ref Listed Drug: MICRO K Firm: KV PHARMACEUTICAL ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route, active ingredient) For products subject to PREA a wavier request must be granted prior to approval of ANDA. Wavier Granted:	☑
Sec. III	**Patent Certification** 1. Paragraph: I ✓ 2. Expiration of Patent: NA A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement:** YES	☑
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓ Bottles of 100/(CRC), 500	☑
Sec. V	**Labeling** (Mult Copies N/A for E-Submissions) e-labeling provided 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓ 4. Was a proprietary name request submitted? (If yes, send email to Labeling Rvwr indicating such.)	☑
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES ✓ **2. Request for Waiver of In-Vivo Study(ies): YES ON 600 MG EQ TO 8 MG** ✓ porportional **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) **4. Lot Numbers of Products used in BE Study(ies):** Ref# 030274 (8mEq) 50167 (10mEq) **5. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING ON 750 MG EQ TO 10 MG fed study not required per Biofile a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) ok per report summary b. EDR Email: Data Files Submitted: YES SENT TO EDR c. In-Vitro Dissolution: YES complete	☑

Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO a. <u>Solutions</u> (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. <u>Suspensions</u> (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. EDR Email: Data Files Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. EDR Email: Data Files Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** ✓ 1. Unit composition and batch formulation ✓ 2. Inactive ingredients as appropriate ✓ ok per IIG (see attached)	☑ ✓

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ # (b) (4) b. Type II DMF authorization letters or synthesis c. COA(s) specifications and test results from drug substance mfgr(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified ✓ b. Testing specifications (including identification and characterization) ✓ c. Suppliers' COA (specifications and test results) ✓ d. Applicant certificate of analysis ✓	☑
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ✓ 2. CGMP Certification: YES 3. CFN numbers	☑
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions ✓ (inactives only) 3. CGMP Certification/GLP 4. CFN numbers	☑
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation, if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified → 3.If sterile product: Aseptic fill / Terminal sterilization 4.Filter validation (if aseptic fill) 5. Reprocessing Statement ✓	☑
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation → 2. In-process Controls - Specifications and data	☑
Sec. XIII	**Container** (b) (4) (CCEC) 1. Summary of Container/Closure System (if new resin, provide data) 2. Components Specification and Test Data (Type III DMF References) 3. Packaging Configuration and Sizes 4. Container/Closure Testing 5. Source of supply and suppliers address lacks schematic drawing for (b) (4) cc bottle (b) (4)	☑

Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data ✓ 2. Certificate of Analysis for Finished Dosage Form ✓	☑
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted complete a. 3 month accelerated stability data ✓ b. Batch numbers on stability records the same as the test batch ✓	☑
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers	☑
Sec. XVII	**Environmental Impact Analysis Statement** Yes	☑
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature): YES 3. List of Convictions statement (original signature) yes	☑

8 mEq ↑ (b) (4)

10 mEq ↑ (b) (4)

see reconciliation attached — varies due to weight conversions

8mEq

TY= (b) (4)

AY=

AP=

10mEq

TY= (b) (4)

AY=

AP=

ANDA 77-419 Final Check List for Branch Chief

✓ 1) Check letter date and stamp date of ANDA vs. drafted letter.

✓ 2) Check for any NC arriving post stamp date but prior to Reg. Review.

✓ 3) Check for gross errors in letter.

✓ 4) Check that correct letter format is used. (PIV vs. Other acknowledgment)

✓ 5) Check address and contact person on letter vs. 356h.

✓ 6) Check for any t-cons and verify date and correspondence date.

✓ 7) Check Patent Certification information in entered in COMIS (by Eda) vs. Actual certification. If multiple patent certifications, should be based on PIV if applicable or latest expiring patent.

✓ 8) Check for any comments or problems raised by reviewer on Check List.

N/A 9) If first generic, copy BE review and file.

✓ 10) Sign Check List.

✓ 11) Check electronic Orange Book to verify current patent information and correct RLD. Microk 10

✓ 12) Check for MOU patents

✓ 13) Review 356h. Check NDA number and RLD for correct reference. If proprietary name proposed, notify Labeling reviewer.

✓ 14) Review Basis for Submission. Microk/Microk 10 18-238

✓ 15) Review Patent Certifications and Exclusivity Statement. (If an expiration of an exclusivity has occurred make a note to the Labeling reviewer.

✓ 16) Review Comparison between Generic Drug and RLD for: condition of use, active ingredients, route of administration, dosage form and strength. Check Components and Composition.

✓ 17) Sign cover letter 505 (j)(2)(A) OK, date, and full signature.

✓ 18) Pull USP information. (USP ____yes ____no)

✓ 19) Final Grammar review on letter.

✓ 20) Verify information in OGD Patent Tracking System.

✓ 21) EES slip.

✓ 22) Document in record book.

Signature Martin H. Johnson date 24 JAN 2005

Andrx
PHARMACEUTICALS
LLC

ANDA 77-419
Potassium Chloride Extended-release Capsules USP, 8 mEq & 10 mEq

January 11, 2005

NAI
Camphire
1/25/05
N/mc

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: TELEPHONE REQUEST

Dear Mr. Buehler:

Reference is made to the above-referenced Abbreviated New Drug Application (ANDA) and to my January 11, 2004 telephone conversation with Arianne Camphire, Office of Generic Drugs (OGD).

As requested, Andrx is hereby submitting the schematic drawing for the 500 count bottle (b) (4) cc), product code (b) (4), the updated Environmental Consideration statement and Environmental Impact – Claim of Categorical Exclusion to reference the correct citation, 21 CFR 25.31 (a).

Should you have any questions concerning this submission, please do not hesitate to contact the undersigned at (954) 358-6125 (telephone) or (954) 358-6350 (fax).

Sincerely,

Janet Vaughn
Director of Regulatory Affairs

RECEIVED
JAN 13 2005
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx
PHARMACEUTICALS
LLC

77-419

December 1, 2004

Gary Buehler,
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Potassium Chloride Extended-release Capsules USP, 8 mEq & 10 mEq

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Dear Sir:

In accordance with Section 505(j) of the FD&C Act and 21 CFR 314.94, Andrx Pharmaceuticals is submitting an original Abbreviated New Drug Application for approval to market its formulation of Potassium Chloride Extended-release Capsules USP, 8 mEq & 10 mEq. The reference listed drug is Micro K® / Micro K® 10 EXTENCAPS® (Potassium Chloride Extended-release Capsules, USP) 600 mg (8 mEq K) / 750 mg (10 mEq K), manufactured by KV Pharmaceutical.

This application consists of six (6) volumes and contains the necessary information to demonstrate that Andrx' generic product is both pharmaceutically equivalent and bioequivalent to the reference listed drug. Two copies of the application are provided, an archival copy (in blue folders), which contains all the information required for the ANDA, and a technical review copy (in red folders), which contains all the information in the archival copy except the Bioequivalence section (Section VI). A separate copy of the Bioequivalence section is provided in orange folders. An "Executive Summary" of the application follows this cover letter.

Additionally, concurrently with the filing of this ANDA, a true copy of the technical review copy with the exception of the Bioequivalence section (VI) of the ANDA (including a copy of Form FDA 356h and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) was sent to our local district office. This "field copy" was contained in a burgundy folder.

This application contains an electronic submission of labeling data. The draft package insert is provided in Microsoft Word 2000 and PDF format on a compact disk located with the four copies of the draft labeling in the Chemistry Review Copy. The data contained in the electronic submission is the same as in the hardcopy submission.

Andrx Pharmaceuticals commits to resolve any issues identified in the methods validation process after approval. Please direct any written communications regarding this ANDA to me at the above address. My email address is janet.vaughn@andrx.com. I may also be reached at (954) 358-6125 (*direct dial*), (954) 214-0145 (*cell*) or (954) 358-6350 (*fax*).

Sincerely,

Janet Vaughn
Director of Regulatory Affairs

RECEIVED
DEC 0 2 2004
OGD / CDER