

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74726**

**BIOEQUIVALENCY REVIEW(S)**



Potassium Chloride ER Tablets  
Klor-Con, 20 mEq  
ANDA #74-726/~~4011~~  
Reviewer: Nhan L. Tran  
Filename: 74726d.898

Upsher-Smith  
Minneapolis, MN  
Submission date:  
August 20, 1998

Review of an Amendment

I. Objective

Review of Upsher-Smith's revised dissolution data for its Potassium Chloride ER Tablets, 20 mEq.

II. Background Information

Upsher-Smith's bioequivalence study on its Potassium Chloride ER Tablets, 20 mEq, was reviewed by the Division of Bioequivalence (M. Kochhar). The in-vivo bioequivalence study and in-vitro dissolution testing were found acceptable. The firm was notified in an Agency letter dated 9/6/1996 of the dissolution specifications as follows:

Time, hrs	Dissolution Specifications
1	NMT %
2	NLT % and NMT %
6	NLT % and NMT %
12	NLT %

Based on the results from the half tablet dissolution data, the Division recommended the specification for 1 hour to be changed from NMT % to NMT % (Letter date: March 3, 1997). The firm submitted additional data on November 7, 1997 to show that NMT % is too stringent and wanted to change to % by submitting dissolution testing data on additional batches of the test product using 6 tablets, and data for the bio batch using 12 tablets.

The 1-hour dissolution data for a total of 66 tablets were tabulated as follows:

% Dissolved	# of Tablets
	8
	27
	29
	2
	66 tablets

The firm considers that NMT % at 1 hour point is appropriate for their quality control purposes. The Division considers that their data supported the claim. The Division also recommends NLT % as the lower limit at 1 hour time point. The new dissolution specifications were faxed to the firm on June 18, 1998 as follows:

Time, hrs	Dissolution Specifications
1	NLT % and NMT %
2	NLT % and NMT %
6	NLT % and NMT %
12	NLT %

### III. Review of the amendment

In the present amendment, the firm informs the Agency that it agrees to make the modifications as recommended by the Division of Bioequivalence. The firm indicates that these specifications are for release testing only AND THAT THE ROUTINE STABILITY TESTING WILL REMAIN AS LISTED IN THEIR CURRENT APPLICATION. The reviewer, after discussing the issue with the OGD review chemist (J. Fan) and Team Leaders (M. Smela and V. Sayeed), we all agreed that these specifications should be for release testing AND ROUTINE STABILITY TESTING.

IV. Recommendation

The Division of Bioequivalence acknowledges Upsher-Smith's agreement to the release specifications recommended by the Division for release testing. These specifications should also be used for stability testing as well.

The Division of Bioequivalence recommends dissolution testing should be incorporated into the firm's **manufacturing controls and stability programs**. The dissolution testing should be conducted in 900 mL of deaerated water at 37° C using USP XXIII apparatus 2 (Paddle) at 50 rpm, and the test should meet the following specifications:

Time, hrs	Dissolution Specifications
1	NLT 10% and NMT 15%
2	NLT 10% and NMT 15%
6	NLT 10% and NMT 15%
12	NLT 10%

The firm and OGD Chemistry Division I (Reviewer: J.Fan, Team Leader: V. Sayeed) should be informed of the recommendation.

Review Branch 11  
Nhan L. Tran, Ph.D.  
Division of Bioequivalence

RD INITIALED BY SNERURKAR  
FT INITIALED BY SNERURKAR

Concur: \_\_\_\_\_  
Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence

CC: ANDA 74-726/A-011, HFD 655 (Nerurkar, Tran), Drug File, Division File.

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

Potassium Chloride ER Tablets	Upsher-Smith
20 mEq	Minneapolis, MN
ANDA #74-726 ✓	Submission date: 11/7/1997
Reviewer: Moo Park	
REF PRODUCT	n/a
BE STUDY DESIGN	n/a
STUDY RESULTS	n/a
DISSOLUTION	Dissolution specifications at 1 hour were recommended as NLT % and NMT % based on the dissolution data submitted by the sponsor.
WAIVER	n/a

INITIAL:   /  S  /    
 REVIEWER: Moo Park, Ph.D.  
 BRANCH: III

DATE:   3/12/98  

INITIAL:   /  S  /    
 TEAM LEADER: Moheb Makary, Ph.D.  
 BRANCH: III

DATE:   3/12/98  

INITIAL:   /  S  /    
 DIRECTOR: Dale P. Conner, Pharm.D.  
 DIVISION OF BIOEQUIVALENCE

DATE:   3/31/98  

INITIAL: \_\_\_\_\_  
 DIRECTOR  
 OFFICE OF GENERIC DRUGS

DATE: \_\_\_\_\_

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-726

APPLICANT: Upsher-Smith

DRUG PRODUCT: Potassium Chloride ER Tablets, 20 mEq

The Division of Bioequivalence has completed its review and has the following recommendation:

The Division of Bioequivalence agrees that the information submitted to the Agency in support of the upper dissolution limit of 35% at one hour time point is acceptable. The Division of Bioequivalence recommends that the dissolution specifications at one hour should be NLT % and NMT %. The following dissolution specifications are recommended.

Time, hrs	Dissolution Specifications
1	NLT 35% and NMT 65%
2	NLT 35% and NMT 65%
6	NLT 35% and NMT 65%
12	NLT 35%

Please note that the bioequivalency 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 bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

*JS*

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

Potassium Chloride ER Tablets      Upsher-Smith  
 20 mEq      Minneapolis, MN  
 ANDA #74-726      Submission date: 11/7/1997  
 Reviewer: Moo Park  
 Filename: 74726d.n97

### Review of an Amendment

#### I. Objective

Review of Upsher-Smith's dissolution data for its Potassium Chloride ER Tablets, 20 mEq. Upsher-Smith requested for a reconsideration of the dissolution specifications based on the new dissolution data submitted in the amendment.

#### II. Background

Upsher-Smith's bioequivalence study on its Potassium Chloride ER Tablets, 20 mEq, was reviewed by Dr. M. Kochhar and the study was acceptable. Dissolution data was also acceptable. The firm was notified in an Agency letter dated 9/6/1996 of the dissolution specifications as shown below:

Time, hrs	Dissolution Specifications
1	NMT %
2	NLT % and NMT %
6	NLT % and NMT %
12	NLT %

The firm submitted dissolution data for half tablets, which were reviewed by Dr. M. Kochhar. After reviewing the half tablet data, the Division lowered the specification for 1 hour from NMT

40% to NMT 30%. The firm submitted additional data to show that NMT 30% is not adequate.

### III. Comments

- The firm conducted dissolution testing on additional 9 batches of the test product using 6 tablets. The firm also added the dissolution data for the bio batch (12 tablets). The 1-hour dissolution data for a total of 66 tablets were tabulated as follows:

% Dissolved	# of Tablets
	8
	27
	29
	2
Total	66 tablets

- The firm considers that NMT % at 1 hour point is adequate for their quality control purposes. The Division considers that their data demonstrated their viewpoint is valid and adequate. The Division also recommends NLT % as the lower limit at 1 hour time point. Therefore, the new dissolution specifications will be as follows:

Time, hrs	Dissolution Specifications		
1	NLT	$\frac{1}{2}$ and NMT	$\frac{1}{2}$
2	NLT	$\frac{1}{2}$ and NMT	$\frac{1}{2}$
6	NLT	$\frac{1}{2}$ and NMT	$\frac{1}{2}$
12	NLT	$\frac{1}{2}$	

- Upsher-Smith's new dissolution specifications meet the USP specifications for Potassium Chloride ER Tablets, USP. The original specifications proposed also met the USP

specifications.

#### IV. Recommendation

The Division of Bioequivalence agrees that the information submitted to the Agency in support of the upper dissolution limit of % at one hour time point is acceptable. The Division of Bioequivalence recommends that the dissolution specifications at one hour should be NLT % and NMT %. The following dissolution specifications are recommended.

Time, hrs	Dissolution Specifications
1	NLT % and NMT %
2	NLT % and NMT %
6	NLT % and NMT %
12	NLT %

The firm should be informed of the recommendation.

*/s/*  
 Moo Park, Ph.D.  
 Chemist, Review Branch III  
 Division of Bioequivalence

RD INITIALED MMAKARY  
 FT INITIALED MMAKARY

Concur: */s/*

Dale P. Conner, Pharm.D.  
 Director  
 Division of Bioequivalence

Date: 3/31/98

File history: Draft (3/6/98); Final (3/12/98)

FEB 26 1997

1

Potassium Chloride  
1500 mg (20 mEq) Extended-release  
Tablets  
Klor-Con M20  
ANDA # 74-726  
Reviewer: Man M. Kochhar

Upsher-Smith Laboratories  
Minneapolis, MN  
Submission Date:  
August 8, 1995 and  
February 12, 1997

Response to an Amendment Dated January 3, 1997

The bioequivalence study and dissolution testing on the whole tablet was found to be acceptable (see review by Dr. Kochhar, Division Date May 2, 1996). However, 20 mEq tablet is a scored ER tablet, therefore, the firm has submitted the content uniformity and the comparative dissolution testing on half tablets. The results are presented in Table 1. The result showed that the dissolution testing on half tablet meets the specification and therefore, the study is acceptable.

RECOMMENDATION:

1. The bioequivalence study conducted by Upsher-Smith Laboratories on its Potassium Chloride Extended-release 20 mEq tablets lot # 15112, comparing it to K-Dur 20, lot # 93772, manufactured by Key Pharmaceuticals has been found acceptable by the Division of Bioequivalence. The study demonstrates that Upsher-Smith's Potassium Chloride Extended-release tablets, 20 mEq are bioequivalent to the reference product, K-Dur 20 mEq tablets, manufactured by Key Pharmaceuticals.
2. An acceptable dissolution on whole tablet was provided with the original submission. The in vitro test results on half tablets are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of deaerated water at 37° C using USP XXIII apparatus 2 (Paddle) at 50 rpm. The test should meet the following specifications:

1 Hour			NMT	%
2 Hours	NLT	% and	NMT	%
6 Hours	NLT	% and	NMT	%
12 Hours	NLT	%		

From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution test, and therefore, the application is acceptable.

The firm should be informed of the recommendations.

/S/  
Man M, Kochhar, Ph.D  
Review Branch III  
Division of Bioequivalence

RD INITIALLED RMHATRE  
FT INITIALLED RMHATRE \_\_\_\_\_ /S/ \_\_\_\_\_ Date: 2/25/97  
Ramakant M. Mhatre, Ph.D.  
Chief, Review Branch III

Concur: \_\_\_\_\_ /S/ \_\_\_\_\_ Date: 2/26/97  
Rabindra Patnaik, Ph.D.  
Acting Director  
Division of Bioequivalence

MMKochhar/mmk/2-18-97; 2-25-97; 74-726 BIO Response

cc: ANDA # 74-726 original, HFD-630, HFD-600 (Hare), HFD-658 (Mhatre, Kochhar), Drug File, Division File.

Table 1. In Vitro Dissolution Testing						
Drug (Generic Name): Potassium Chloride Extended-Release Tablets Dose Strength: 20 mEq ANDA No.: 74-726 Firm: Usher-Smith Submission Date: June 20, 1996 File Name:						
I. Conditions for Dissolution Testing for Half Tablet:						
USP XXIII Basket: Paddle: X RPM 50 No. Units Tested: 12 Medium: Volume: 900 Deaerated Water Specifications: 1 Hour NMT % 2 Hours NLT % NMT % 6 Hours NLT % and NMT % 12 Hours Not Less Than % Reference Drug: K-Dur  Assay Methodology:						
II. Results of In Vitro Dissolution Testing:						
Sampling Times (Hours)	Test Product Lot # 15112 Strength 20 mEq			Reference Product Lot # 93772 Strength 20 mEq		
	Mean %	Range	%RSD	Mean %	Range	%RSD
1	27.1		4.1	22.4		9.6
2	39.8		4.0	40.9		6.4
6	75.7		4.3	78.6		7.1
12	94.5		4.5	99.3		3.0

Content Uniformity: Test Product, 99.8%; RSD % 3.8  
Reference Product, 102.5%; RSD% 4.9

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-726

SPONSOR: *Upsher-Smith*

DRUG: KCl ER

DOSAGE FORM: Tablet

STRENGTH(s): 20mEq

TYPE OF STUDY: Single/Multiple

Fasting/Fed

STUDY SITE: *Phoenix International*

STUDY SUMMARY: This study was designed to compare the single-dose bioavailability of test and reference microencapsulated ER tablets. This study design was to control diet & 4500 mL of fluids/day for 1st three days (on day 4 & 5 there was a blood draw, urine collection & controlled diet & 4500 mL of water). On day 6 & 7 a single dose of 4x 20 mEq of test & Ref. product was given. On day 7, 9, 10, 11 & 12 blood draw and day 8 & 12 36-48 hr urine collection. Total amount of K excreted in urine with baseline correction was comparable for test & Ref. Pharmacokinetic Parameters were comparable and study was acceptable.

DISSOLUTION: 900 mL of water, apparatus 2 (Puddle) at 50 rpm. 1 Hr - NMT  $\geq 0$   
2 Hr - NLT  $\geq 0$  - NMT  
6 Hr - NLT  $\geq 0$  - NMT  
12 Hr - NLT  $\geq 0$

PRIMARY REVIEWER:

*IS*

BRANCH: III

INITIAL: *IS*

DATE: 7/29/96

BRANCH CHIEF:

BRANCH:

INITIAL: *IS*

DATE: 8/28/96

DIRECTOR  
DIVISION OF BIOEQUIVALENCE

*for*

INITIAL: *IS*

DATE: 8/28/96

DIRECTOR  
OFFICE OF GENERIC DRUGS

INITIAL: *IS*

DATE: 1/28/96

*revised  
1/28/96  
J. P. ...  
3/4*

# OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-726

SPONSOR : *Upsher Smith*

DRUG & DOSAGE FORM : *Potassium Chloride ER Tablet*

STRENGTH (s) : *20 mEq*

TYPE OF STUDY: SD SDF MULT OTHER

STUDY SITE: CLINICAL : ANALYTICAL :

STUDY SUMMARY :

*Amendment*

Parameter	test	ref	ratio	90% CI (log).
Cmax (ng/ml)				

AUC(0-T) ngxhr/ml

AUC(0-Inf) ngxhr/ml

Tmax hr

Half-life hr

DISSOLUTION : *of 1/2 Tablet*

Conditions

Time (min)	Test Mean (range)	Ref. Mean (range)
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15 1Hr	27.1 ( )	22.4 ( )
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30 2Hr	39.8 ( )	40.9 ( )
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<del>45 6Hr</del>	<del>75.7 ( )</del>	<del>78.6 ( )</del>
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12 Hr	94.5 ( )	99.3 ( )
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Q = 1Hr NMT	%	%
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2Hr NLT	% - NMT	%
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6Hr NLT	%	%
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12Hr NLT	%	%
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PRIMARY REVIEWER : *MMK*      BRANCH : *III*

INITIAL :    */S/*         DATE :    *2/26/97*   

BRANCH CHIEF : \_\_\_\_\_      BRANCH : \_\_\_\_\_

INITIAL :    */S/*         DATE :    *2/25/97*   

DIRECTOR  
DIVISION OF BIOEQUIVALENCE

INITIAL :    */S/*         DATE :    *2/26/97*   

DIRECTOR  
OFFICE OF GENERIC DRUGS

INITIAL : \_\_\_\_\_      DATE : \_\_\_\_\_

AUG 27 1996

1

Potassium Chloride  
Extended-release  
20 mEq Tablets  
Klor-Con M10 & Klor-Con M20  
ANDA # 74-726  
Reviewer: Man M. Kochhar

Upsher-Smith Laboratories  
Minneapolis, MN  
Submission Date:  
June 20, 1996

### Review of an Amendment

#### BACKGROUND

The firm has submitted an acceptable bioequivalence study on potassium chloride extended release 20 mEq tablets on August 8, 1995. At that time application was incomplete for 20 mEq tablets due to inappropriate dissolution method. A waiver for 10 mEq tablets was not granted. The firm has withdrawn the waiver request for their 10 mEq tablet and has submitted new dissolution data for 20 mEq tablets.

#### DISSOLUTION

In-vitro dissolution testing was conducted in 900 mL of deaerated water at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. Sampling was done at 1, 2, 6, and 12 hours. Results are presented in Table 1.

The sponsor has also conducted dissolution testing in 900 mL of intestinal fluid without enzymes using USP XXIII apparatus 2 (paddle) at 50 rpm. Sampling was done at 1, 2, 6, and 12 hours. Results are presented in Table 2.

#### RECOMMENDATIONS:

1. The fasting, non-fasting and multiple-dose bioequivalence studies conducted by Upsher-Smith Laboratories on its Potassium Chloride Extended-release 20 mEq tablets lot # 15112, comparing them to K-Dur 20, lot # 93772, manufactured by Key Pharmaceuticals has been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting, non-fasting and multiple-dose conditions the Usher-Smith's Potassium Chloride Extended release tablets, 20 mEq are bioequivalent to the reference product, K-Dur 20 mEq tablets, manufactured by Key Pharmaceuticals.
2. The in-vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted on 12 tablets in 900 mL of deaerated water at 37°C using USP XXIII apparatus 2 (Paddle) at 50 rpm. The test should meet the following specifications:

1 hour		NMT	%
2 hours	NLT : % and	NMT	%
6 hours	NLT : % and	NMT	%
12 hours	NLT : %		

The firm should be informed of the recommendations.

*MS*

Man M, Kochhar, Ph.D  
Review Branch III  
Division of Bioequivalence

RD INITIALLED RMHATRE  
FT INITIALLED RMHATRE

*MS*

*8/1/96*

*MS*

Concur:

*[Signature]*  
Keith K. Chan, Ph.D.  
Director  
Division of Bioequivalence

Date:

*8/27/96*

MMKochhar/mmk/7-9-96; 7-24-96; 7-29-96; 74-726 BIO Amendment

cc: ANDA # 74-726 original, HFD-630, HFD-600 (Hare), HFD-344 (Cviswanathan), HFD-658 (Mhatre, Kochhar), Drug File, Division File.



**TABLE 2****1. Conditions for Dissolution Testing**

USP XXIII Apparatus 2 (Paddle) at 50 rpm

Units: 12

Medium: 900 mL of Simmulated Intestinal Fluid w/o enzymes

Specifications:

1 hour			NMT	%
2 hours	NLT	% and	NMT	%
6 hours	NLT	% and	NMT	%
12 hours	NLT	%		

**2. Results:**

Sampling Times (Hours)	Test Product Lot # 15112 20 me Tablets			Reference Product Lot # 93772 20 me Tablets		
	Mean	Range	%RSD	Mean	Range	%RSD
1	24.3		3.5	21.7		10.1
2	36.9		2.9	37.5		8.6
4	58.9		1.6	65.3		4.5
6	72.7		1.2	79.6		3.0
8	83.3		1.2	88.5		2.7
10	89.6		1.2	94.4		1.7
12	94.3		1.0	99.6		1.1

Potassium Chloride  
Extended-release 10 mEq  
and 20 mEq Tablets  
Klor-Con M10 & Klor-Con M20  
ANDA # 74-726  
Reviewer: Man M. Kochhar

Upsher-Smith Laboratories  
Minneapolis, MN  
Submission Date:  
August 8, 1995

Review of a Bioequivalence Study and Dissolution  
and a Waiver Request

OBJECTIVE:

The objective of this study was to compare the single-dose bioavailability of Upsher-Smith and Key (K-Dur 20) microencapsulated extended release tablets containing 1500 mg of potassium chloride- equivalent to 20 mEq of potassium per tablet in healthy subjects under fasting, non-fasting and steady state conditions.

INTRODUCTION:

Potassium chloride (KCl) is an electrolyte replenisher, and is indicated for the treatment or prevention of hypokalemia in certain patients. Normal dose of extended-release tablets range from 20 to 100 mEq or more of potassium daily.

The oral bioavailability of KCl preparations can be difficult to determine. Potassium ion ( $K^+$ ) is the principal intracellular cation of most body tissues, and its intracellular and plasma concentrations are maintained within narrow ranges by active ion transport. Thus, the bioavailability of an oral KCl preparation cannot be accurately determined by measuring post-dose plasma  $K^+$  concentrations. Researchers have used urinary excretion of potassium as an indicator of gastrointestinal absorption; urine is the major route of elimination for potassium, and under steady state conditions in normal subjects, the amount of potassium supplied by the diet is equal to the amount excreted in the urine.

The design of this study conforms closely to a previous bioavailability study performed with K-Dur 20 extended-release tablets. The first days of each period will be diet equilibration days, during which the subjects' intake of potassium, sodium, calories and fluids will be established within optimum limits. Diet equilibration will be followed by two days of baseline urinary  $K^+$  measurements, so that the potassium levels measured after drug administration may be corrected for baseline levels. The mean corrected urinary potassium excretion parameters similar to the following may be expected after a single administration of extended-release KCl tablets equivalent to 80 mEq of potassium ( $\pm$ S.D.):

Rmax (mEq/hr)	4.5 ± 2.6
Tmax (hours)	5.5 ± 1.7
0-24 hr Cumulative Excretion (mEq)	40.4 ± 16.5

#### IN-VIVO STUDY:

The objective of this study was to compare the single-dose bioavailability of Upsher-Smith and Key (K-Dur 20) microencapsulated extended release tablets containing 1500 mg of potassium chloride-equivalent to 20 mEq of potassium per tablet. The bioequivalence study was conducted by \_\_\_\_\_ under the supervision of \_\_\_\_\_

#### STUDY DESIGN:

Open-label, randomized, two-way crossover study.

#### OUTLINE OF STUDY DESIGN

Day 1	Controlled Diet, 4500 mL of fluid throughout the day.
Day 2	Controlled Diet, 4500 mL of fluid throughout the day.
Day 3	Controlled Diet, 4500 mL of fluid throughout the day.
Day 4	One Blood Draw, Urine Collection, Controlled Diet, 4500 mL of fluid throughout the day.
Day 5	One Blood Draw, Urine Collection, Controlled Diet, 4500 mL of fluid throughout the day.
Day 6	Dosing between 7:00 - 8:00 AM, One Blood draw, Urine Collection, Controlled Diet, Stool Sample, 4500 mL of fluid throughout the day.
Day 7	One Blood Draw, Urine Collection, Controlled Diet, 4500 mL of fluid throughout the day.
Day 8	36-48 hour Urine Collection, Controlled Diet 4500 mL of fluid throughout the day.
Day 9	One Blood draw, Urine Collection, Controlled Diet, 4500 mL of fluid throughout the day.
Day 10	One blood Draw, Urine Collection, Controlled Diet 4500 mL of fluid throughout the day.
Day 11	Dosing between 7:00 - 8:00 AM, One blood draw, Urine Collection, Controlled Diet, 4500 mL of fluid throughout the day.

Day 12 One Blood Draw, Urine Collection, Controlled Diet,  
4500 mL of fluid throughout the day.

36 - 48 urine Collection; Released between 8:00 - 9:00 AM

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Subjects:

The study employed thirty two (32) healthy volunteers between the ages of 18-45, whose weight did not deviate by more than  $\pm 15\%$  of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin, 1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests ( blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications and/or OTC preparations for at least 7 days prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products throughout the study. Each subject signed a written informed consent.

The subjects remained in the clinic from 10 hours before the drug administration till the end of urine collection on Day 13.

Methods:

The product and dosage employed in this study were as follows:

Treatment A. Test: Four 20 mEq extended-release tablets of potassium chloride (Klor-Con 20M), lot # 15112 with 500 mL of water between 7:00 and 7:58 a.m. on Study Day 6 (Period 1) and Day 11 (Period 2).

Batch size: , Expiry Date: n/a

Treatment B. Reference: Four 20 mEq extended-release tablets of potassium chloride ( K-Dur 20; Key), lot # 93772, with 500 mL of water between 7:00 and 7:58 a.m. on Study Day 6 (Period 1) and Day 11 (Period 2).

Exp. 4-95

**Blood Collection:**

Blood samples ( 1 x 5 mL ) were collected prior to the end of each 24 hour urine collection interval for day 4, 5, 6 ( 0-24 and 24-48 hour intervals), 9, 10, and 11 (0-24 and 24-48 hour intervals), for the determination of serum creatinine.

**Urine Collection:**

Urine was collected on Study Days 4, 5, 9, and 10 for predose baseline potassium measurements. On Study Days 6-8 and 11-13, urine was collected for post-dose potassium measurements. The following collection intervals were used:

<u>STUDY DAYS</u>	<u>COLLECTION INTERVALS</u> (hours after 7:00 a.m./Dosing)
4*, 5*, 9*, 10	0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-24
6, 11	0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-24, 24-36, 36-48

\* Subjects were asked to void shortly before the 1st schedule urine collection interval (0-1 hr) began on days 4 and 9. This urine was not collected.

**Stool Collection:**

Post-dose stool samples were collected on each dosing day ( Days 6 and 11) and the following day (Days 7 and 12), in order to test for stool occult blood. All results were negative except for Subject No.25 result on Day 6 which the study physician judged to be not clinically significant.

**Water Administration:**

From Day 1 to Day 12 of the study, 4500 mL of water or other fluids were administered per day to each subject according to the following schedule. No other intake of fluids was allowed.

<u>Volume of Liquid</u> (mL)	<u>Time of Administration</u> (Hours after 7:00 a.m.)
500	0, 1*, 5*, 10*
250	2, 3, 4, 6, 8, 9, 11, 12, 13, 15*

\* liquid given as fluid other than water.

**Fasting/Meals:**

Subjects received a strictly controlled low-potassium, low-sodium diet of approximately 3500 calories daily with potassium intake of approximately 50-60 mEq per day and sodium intake of approximately 160-180 mEq per day. All subjects completed their meals.

**Creatinine Clearance:**

To ensure that urine collection was complete for each subject, individual 24-hour creatinine clearance were determined for every day of urine collection. Creatinine clearance ( which varied from 1.04 mL/s to 2.28 mL/s or 62.4 mL/min to 136.8 mL/min) were found to be either within the expected range or not clinically significant.

**WASHOUT PERIOD:** 5 days between doses.

**ANALYTICAL METHODOLOGY:****ASSAY VALIDATION:**

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secret and/or

confidential

commercial

information

*Analytical methodology*

**IN VIVO BIOEQUIVALENCE STUDY RESULTS:**

Of the thirty two (32) subjects enrolled in the study, one did not complete the crossover. Subject # 7 elected to withdraw himself from the study for personal medical reasons during the evening of Day 10. As indicated in the Protocol, statistical and pharmacokinetic analyses were performed on data from 30 subjects (Subject # 1-6 and 8-30, and 32). Subject No. 31 and 32 were alternates, and subject No. 32 was used to replace subject # 7 because their sequences were identical, allowing for a balanced number of subjects in each sequence. Concentration-time profiles, rate of excretion and pharmacokinetic parameters for all subjects are in Table 1, 2, and 3, while the mean concentration-time profiles are provided in Figure 1.

**TABLE 1**

**Mean Total Amount (mEq) (Without Baseline Correction) of  
K Excreted in Urine (N=30)**

<b>Time (hours)</b>	<b>Test (CV%)</b>	<b>Ref. (CV%)</b>	<b>T/R</b>
0-1	3.6386 (45)	3.5870 (48)	1.01
1-2	4.2141 (37)	4.2552 (43)	0.99
2-4	7.5220 (35)	8.1737 (53)	0.92
4-6	12.4409 (23)	13.7677 (21)	0.90
6-8	11.2203 (36)	12.2695 (23)	0.91
8-12	16.4620 (23)	17.8100 (25)	0.92
12-16	8.3645 (24)	8.0036 (31)	1.04
16-24	10.5196 (26)	10.1234 (23)	1.04
24-36	30.2318 (20)	30.5655 (22)	0.99
36-48	12.5764 (25)	13.6772 (24)	0.92

**Mean Total Amount (mEq) (With Baseline Correction) of  
K Excreted in Urine (N=30)**

0-1	1.3404 (91)	1.1618 (120)	1.15
1-2	2.0884 (71)	2.2027 ( 62)	0.95
2-4	3.9421 (69)	4.8438 ( 81)	0.82
4-6	6.9814 (37)	7.9226 ( 40)	0.88
6-8	8.0162 (44)	8.8933 ( 28)	0.90
8-12	10.7745 (33)	11.9343 ( 36)	0.90
12-16	3.2415 (57)	2.6411 ( 71)	1.23
16-24	3.1735 (81)	2.3617 ( 60)	1.34
24-36	7.8770 (65)	7.6610 ( 65)	1.03
36-48	0.1074 (239)	0.5529 (447)	0.19

TABLE 2

Rate of Excretion (mEq/hr) (Without Baseline Correction) (N=30)

Time (hours)	Test (CV%)	Ref. (CV%)	T/R
0-1	3.6386 (45)	3.5870 (48)	1.01
1-2	4.2141 (37)	4.2552 (43)	0.99
2-4	3.7610 (35)	4.0868 (53)	0.92
4-6	6.2204 (23)	6.8838 (21)	0.90
6-8	5.6101 (36)	6.1348 (23)	0.91
8-12	4.1155 (23)	4.4525 (25)	0.92
12-16	2.0911 (24)	2.0009 (31)	1.04
16-24	1.3149 (26)	1.2654 (23)	1.04
24-36	2.5193 (20)	2.5471 (22)	0.99
36-48	1.0688 (25)	1.1398 (24)	0.94

Rate of Excretion (mEq/hr) (With Baseline Correction) (N=30)

0-1	1.3404 (91)	1.1618 (120)
1-2	2.0884 (71)	2.2027 (62)
2-4	1.9711 (69)	2.4219 (81)
4-6	3.4907 (37)	3.9613 (40)
6-8	4.0081 (44)	4.4467 (28)
8-12	2.6936 (33)	2.9836 (36)
12-16	0.8104 (57)	0.6603 (71)
16-24	0.3967 (81)	0.2952 (60)
24-36	0.6564 (65)	0.6384 (65)
36-48	0.0089 (2398)	0.0461 (447)

TABLE 3

Pharmacokinetic Parameters (Without Baseline Correction) (N=30)

	Test (CV%)	Reference (CV%)	90% Confidence Intervals
T <sub>Ae</sub> (mEq)	117.19 (11)	122.23 (11)	92; 99
T <sub>Ae</sub> 0-24 (mEq)	74.38 (14)	77.99 (12)	91; 99
R <sub>max</sub> (mEq/hr)	6.93 (25)	7.44 (24)	86; 100
T <sub>max</sub> (hour)	5.25 (31)	4.88 (31)	
Ln T <sub>Ae</sub> (mEq)	116.44 (11)	121.48 (11)	92; 99
Ln T <sub>Ae</sub> 0-24 (mEq)	73.68 (14)	77.41 (12)	91; 99
Ln R <sub>max</sub>	6.73 (25)	7.25 (23)	86; 100

Pharmacokinetic Parameters (With Baseline Correction) (N=30)

T <sub>Ae</sub> (mEq)	47.54 (25)	50.17 (22)	87; 102
T <sub>Ae</sub> 0-24 (mEq)	39.56 (23)	41.96 (19)	89; 101
R <sub>max</sub> (mEq/hr)	4.78 (29)	4.99 (31)	86; 106
T <sub>max</sub> (hour)	5.85 (35)	6.12 (31)	

Ln TAe (mEq)	45.78 (31)	48.69 (27)	86;	102
Ln TAe 0-24 (mEq)	38.44 (26)	41.06 (22)	87;	101
Ln Rmax (hour)	4.60 (28)	4.81 (27)	87;	105

TAe = Total Urinary Excretion

Rmax = Maximum Excretion Rate

On the basis of in vivo bioavailability data it is determined that Upsher-Smith 20 mEq potassium chloride tablet formulation meets the % bioequivalence criteria for the 90% confidence intervals around the ratios of least-squares means for the ln-transformed TAe, TAe 0-24, and Rmax.

#### DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of deaerated Water at 37°C using USP XXIII apparatus 2 (paddle) at 50 rpm. Sampling was done at 1, 2, 6, and 12 hours. Results are presented in Table 4.

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

#### COMMENTS:

##### 1. Uncorrected (for Baseline) Data

The ratio of least-squares means (with 90% confidence intervals) for the potassium ln-transformed parameters total urinary excretion (TAe), total urinary excretion from 0-24 hours (TAe 0-24), and maximum excretion rate (Rmax) were 95.9% (92 to 99), 95.2% (91 to 99), and 92.7% (86 to 100), respectively. The mean Tmax for the Upsher-Smith product was 5.25 hours, compared with 4.88 hours for the Key product. Results for untransformed parameters showed similar trends.

##### 2. Corrected (for Baseline) Data

The ratio of least-squares means (with 90% confidence intervals) for the potassium ln-transformed parameters total urinary excretion (TAe), total urinary excretion 0-24 hours (TAe 0-24), and maximum excretion rate (Rmax) were 94.0% (86 to 102), 93.6% (87 to 101), and 95.7% (87 to 105), respectively. The mean Tmax for test product was 5.85 hours, compared with 6.12 hours for the reference product. Results for the untransformed parameters showed similar trend.

3. No serious side effects were observed.

4. The sponsor has conducted the dissolution testing in water but dissolution testing in water is incomplete. The sponsor should

provide the dissolution range for each tablet at each time point. In addition to this the firm should also conduct dissolution testing in 900 mL of simulated gastric fluid without enzymes for 0-1 hour and in 900 mL of simulated intestinal fluid without enzymes for 1-8 hours on 12 tablets at 37°C using USP XXIII apparatus 1 (Basket) at 100 rpm.

5. The firm has demonstrated that the formulations of its potassium chloride extended-release tablets, 10 mEq is proportional with respect to active and inactive ingredients (Table 5). The request for waiver for 10 mEq extended-release tablets can not be granted because it is the requirement of the Division of Bioequivalence that all strengths of extended-release tablets must undergo the bioequivalence study. *unless the formulation using a common slow-release granules & directly compressed to make the formulation.*

6. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

*RMM  
5/2/96*

7. The in vivo bioequivalence study is acceptable but the application is incomplete.

#### RECOMMENDATIONS:

1. The application is incomplete. The bioequivalence study conducted by Upsher-Smith Laboratories on its Potassium Chloride Extended-release 20 mEq tablets lot # 15112, comparing it to K-Dur 20, lot # 93772, manufactured by Key Pharmaceuticals has been found acceptable by the Division of Bioequivalence. The study demonstrates that Upsher-Smith's Potassium Chloride Extended release tablets, 20 mEq are bioequivalent to the reference product, K-Dur 20 mEq Tablets, manufactured by Key Pharmaceuticals.

2. The waiver of in vivo bioequivalence study for Upsher-Smith's mEq Potassium Chloride extended-release tablets will not be granted. It is the policy of the Division of Bioequivalence that the firm should conduct bioequivalence study on all strengths of Potassium Chloride extended-release tablets. *unless common slow-release granules was used to compressed the 20 mEq tablets.*

3. The dissolution testing should be conducted on 12 tablets in 900 mL of deaerated water at 37°C using USP XXIII apparatus 2 (Paddle) at 50 rpm. The dissolution testing should also be conducted in 900 mL of simulated gastric fluid without enzymes for 0-1 hour and 900 mL of simulated intestinal fluid without enzymes for 1-8 using USP XXIII apparatus 1 (Basket) at 100 rpm.

*RMM  
5/2/96*

4. The firm should be informed of the recommendations.

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Man.M.Kochhar, Ph.D  
Review Branch III  
Division of Bioequivalence

RD INITIALLED RMHATRE  
FT INITIALLED RMHATRE

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5/2/96

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Concur: \_\_\_\_\_

Date: \_\_\_\_\_

5/2/96

Keith K. Chan, Ph.D.  
Director  
Division of Bioequivalence

MMKochhar/mmk/3-25-96; 4-10-96; 5-1-96; 74-726 BIO

cc: ANDA # 74-726 original, HFD-630, HFD-600 (Hare), HFD-344 (CViswanathan), HFD-658 (Mhatre, Kochhar), Drug File, Division File.

TABLE 5FORMULATIONS

<u>INGREDIENTS</u>	<u>20 mEq</u>		<u>10 mEq</u>	
	<u>%W/W</u>	<u>mg/Tab</u>	<u>%W/W</u>	<u>mg/Tab.</u>
Potassium Chloride, USP				
✓ Croscarmellose Sodium, NF				
Ethylcellulose, NF				
Microcrystalline Cellulose, NF				
Sorbitan Monooleate, NF				
<hr/>				
Total				

Table 4 . In Vitro Dissolution Testing

Drug (Generic Name): Potassium Chloride Extended-Release Tablets  
 Dose Strength: 20 mEq  
 ANDA No.: 74-726  
 Firm: Upsher-Smith  
 Submission Date: August 8, 1995  
 File Name:

## I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50  
 No. Units Tested: 12  
 Medium: Volume: 900 Deaerated Water  
 Specifications: 1 Hour NMT %  
                   2 Hours NLT % and NMT %  
                   6 Hours NLT % and NMT %  
                   12 Hours Not Less Than %  
 Reference Drug: K-Dur

## Assay Methodology:

## II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 15112 Strength 20 mEq			Reference Product Lot # 93772 Strength 20 mEq		
	Mean %	Range	%RSD	Mean %	Range	%RSD
1	27.1			24.1		
2	40.2			43.5		
4	61.9			68.5		
6	77.3			86.4		
12	100.4			107.6		

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Potassium Chloride  
1500 mg (20 mEq) Extended-release  
Tablets  
Klor-Con M20  
ANDA # 74-726  
Reviewer: Man M. Kochhar

Upsher-Smith Laboratories  
Minneapolis, MN  
Submission Date:  
August 8, 1995

**Amendment to Review Dated May 2, 1996**

The bioequivalence study and dissolution testing on the whole tablet was found to be acceptable (see review by Dr. Kochhar, Division Date May 2, 1996). However, 20 mEq tablet is a scored ER tablet, and the firm has not reported content uniformity and the comparative dissolution testing on half tablets. The firm was communicated by telephone to submit comparative dissolution and content uniformity on each half of the tablet. The application is incomplete until the requested information is submitted.

**RECOMMENDATION:**

The firm has not provided comparative dissolution testing and content uniformity data on half tablets of the scored ER Potassium Chloride Tablets. The ANDA 74-726 is, therefore, incomplete. The firm is requested to submit the information.

The firm should be informed of the recommendation.

/S/

Man M, Kochhar, Ph.D  
Review Branch III  
Division of Bioequivalence

RD INITIALLED RMHATRE  
FT INITIALLED RMHATRE

/S/

2/3/97

Ramakant M. Mhatre, Ph.D.  
Chief, Review Branch III

Concur:

/S/

Date:

2/3/97

Rabindra Patnaik, Ph.D.  
Acting Director  
Division of Bioequivalence

MMKochhar/mmk/2-3-97; 74-726 BIO Amendment

cc: ANDA # 74-726 original, HFD-630, HFD-600 (Hare), HFD-658 (Mhatre, Kochhar), Drug File, Division File.